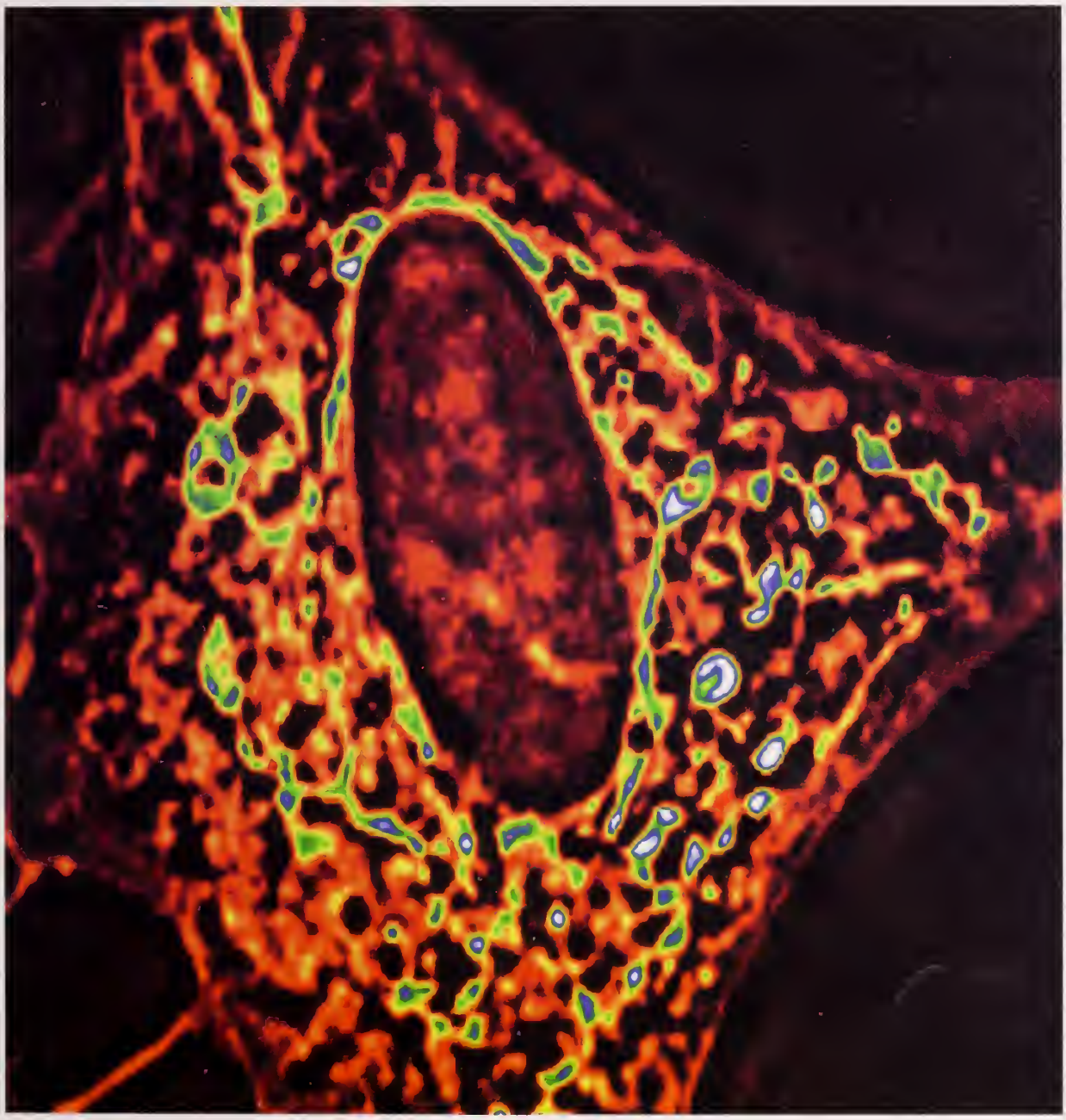
# Weill Graduate School of Medical Sciences of CORNELL UNIVERSITY



1999-2000

# Academic Calendar 1998-99

1998

| | |
|---|---|
| Orientation for new students | Monday, August 24 – Friday, August 28 |
| Opening Exercises | Tuesday, August 25 |
| Registration for **Quarter I** and **Fall Semester** | Wednesday, August 26 – Friday, August 28 |
| **Quarter I** and **Fall Semester** begin | Monday, August 31 |
| Labor Day Holiday observed | Monday, September 7 |
| **Quarter I** ends | Friday, October 23 |
| Examinations for **Quarter I** | Friday, October 23 – Friday, October 30 |
| Registration for **Quarter II** | Friday, October 30 and Monday, November 2 |
| **Quarter II** begins | Monday, November 2 |
| Thanksgiving recess | Thursday-Sunday, November 26-29 |
| Winter recess: Instruction suspended 5:00 p.m. | Saturday, December 19 - Sunday, January 3 |

1999

| | |
|---|---|
| Winter recess ends: Instruction resumed 9:00 a.m. | Monday, January 4 |
| **Quarter II** and **Fall Semester** end | Friday, January 8 |
| Last day for completing requirements for January degrees | Friday, January 15 |
| Conferral of January degrees | Wednesday, January 20 |
| Examinations for **Quarter II** | Friday, January 8 – Friday, January 15 |
| Martin Luther King, Jr.'s Birthday observed | Monday, January 18 |
| Registration for **Quarter III** and **Spring Semester** | Friday, January 15 and Tuesday, January 19 |
| **Quarter III** and **Spring Semester** begin | Tuesday, January 19 |
| Presidents' Day Holiday observed | Monday, February 15 |
| **Quarter III** ends | Friday, March 12 |
| Examinations for **Quarter III** | Friday, March 12 – Monday, March 29 |
| Spring recess | Monday, March 22 – Friday, March 26 |
| Last Day for registering for participation in Commencement | Friday, March 26 |
| Registration for **Quarter IV** | Friday, March 26 and Monday, March 29 |
| **Quarter IV** begins | Monday, March 29 |
| Nineteenth Annual Vincent du Vigneaud Memorial Research Symposium; no classes | Thursday, May 6 |
| Last day of completing requirements for May degrees | Friday, May 21 |
| **Quarter IV** and **Spring Semester** end | Friday, May 21 |
| Examinations for **Quarter IV** | Monday, May 24 – Friday, May 28 |
| Commencement Day, conferral of May degrees, 3:00 p.m., Avery Fisher Hall | Tuesday, May 25 |
| Convocation Ceremony | Tuesday, May 25 |
| Conferral of May degrees | Sunday, May 30 |
| Memorial Day Holiday | Monday, May 31 |

**SUMMER TERM**

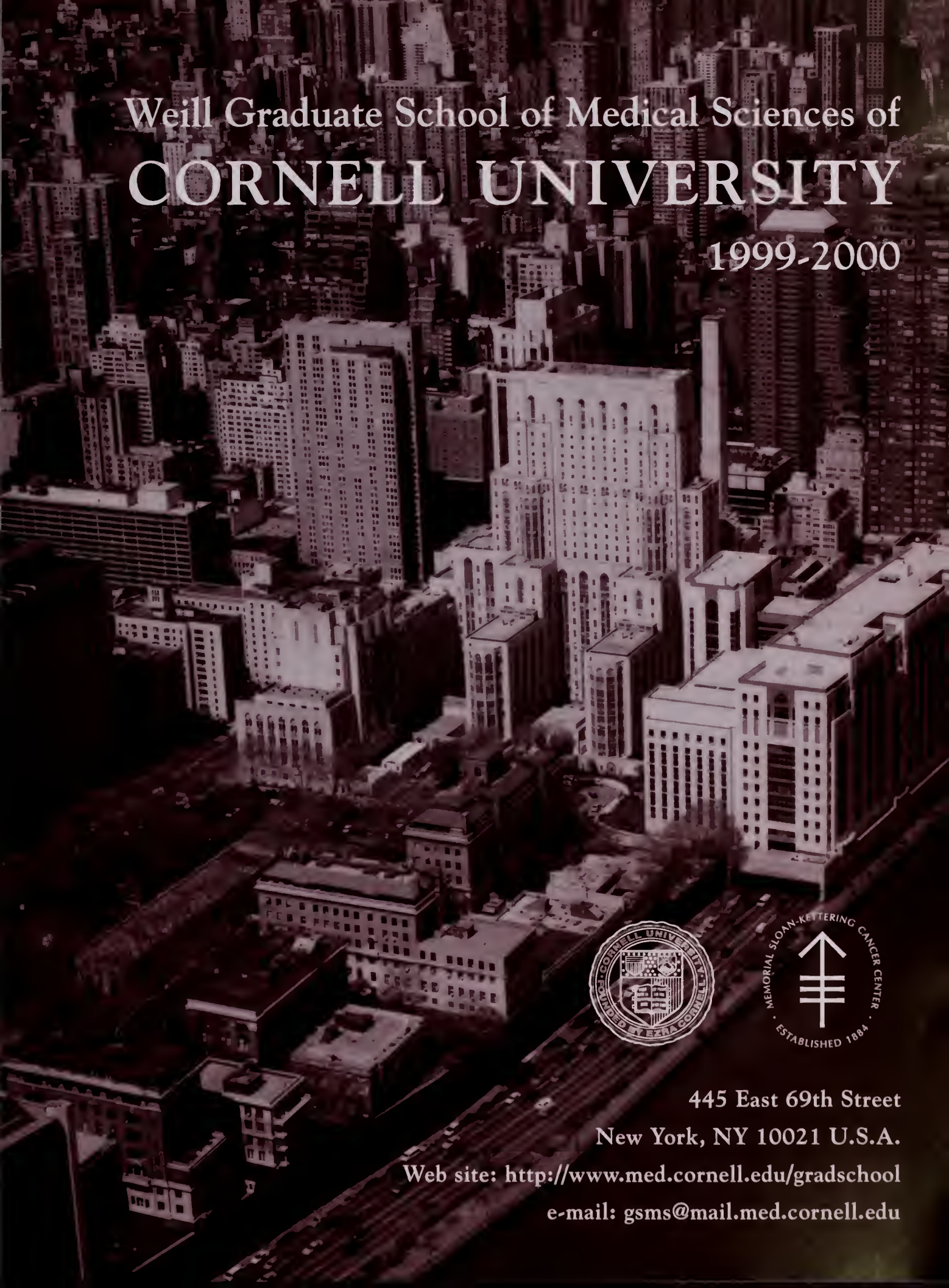
| | |
|---|---|
| Summer research term begins | Wednesday, June 30 |
| Independence Day Holiday observed | Friday, July 2 |
| Last day for completing requirements for August degrees | Friday, August 20 |
| Conferral of August degrees | Monday, August 23 |
| Summer research term ends | Monday, August 30 |

Note: Courses are taught on a quarterly basis, degrees are granted at ends of the Fall, and Spring and Summer terms.

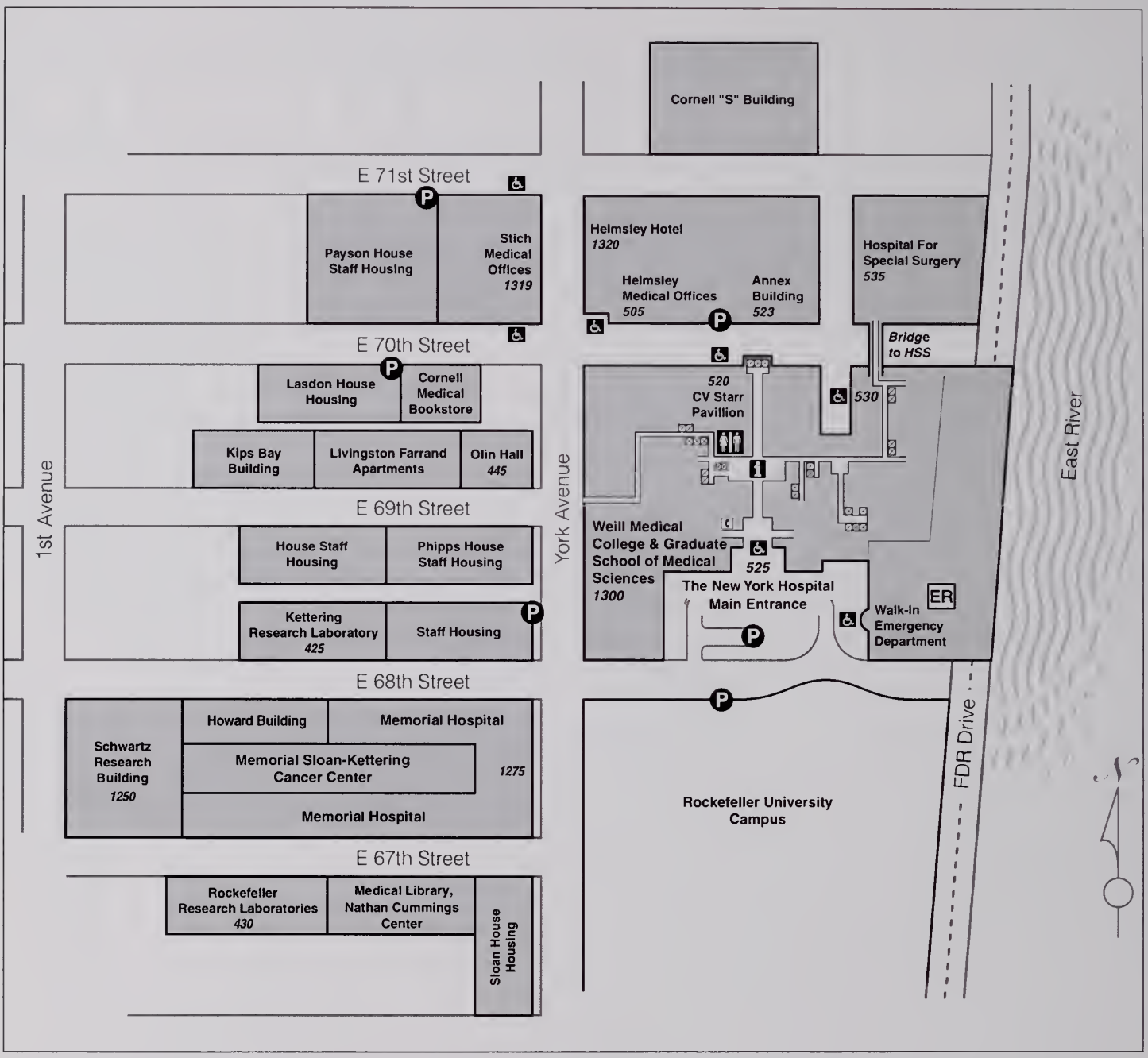
The dates shown in the calendar are subject to change at any time by official action of Cornell University.
In enacting this calendar, the Graduate School of Medical Sciences has scheduled classes on religious holidays. It is the intent of the school that students missing classes due to the observance of religious holidays be given ample opportunity to make up work.

# Weill Graduate School of Medical Sciences of CORNELL UNIVERSITY

1999-2000



445 East 69th Street
New York, NY 10021 U.S.A.
Web site: http://www.med.cornell.edu/gradschool
e-mail: gsms@mail.med.cornell.edu




On the cover: ***Fluorescent indicator of mitochondrial membrane potentials in fibroblasts.***
*Fibroblasts were equilibrated with TMRE. The distribution of this dye in the cell and media follows the Nernst equation. A stack of 25 images was taken and corrected for the out-of-focus light by exhaustive photon reassignment. The corrected image has a resolution of 0.25 μm in x, y and z dimensions.*
*(Photograph courtesy of Gary Gibson and Hui Zhang, Dept. Neurology and Neuroscience), WMC*

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Weill Medical College and Graduate School of Medical Sciences of Cornell University

The Rockefeller Research Laboratories of the Sloan-Kettering Institute

Dear Prospective Student:

This catalog presents the faculty and programs of study of the Joan and Sanford I. Weill Graduate School of Medical Sciences of Cornell University. If we define biomedical science as the pursuit of knowledge in areas of fundamental biology relevant to human health and disease, then the unique resources of our school can indeed provide a superb training opportunity for those interested in the medical sciences. Medicine and biology are in the midst of an unprecedented revolution, which is unraveling the molecular mechanisms governing basic biological processes such as gene replication, intracellular signaling, trafficking of lipid and proteins, neuronal communication, host-defense mechanisms, protein folding, and embryonic development, to name a few. From these insights, new strategies and technologies for addressing the diagnosis and therapy of disease have evolved. Our seven graduate programs offer unique research and educational opportunities for you to master the scientific method of conducting investigative research. We believe that the training opportunities supported by NIH training and research grants will also open doors for rewarding careers in many fields of professional activity including academia, industry, government and health affairs.

The Graduate School of Medical Sciences of Cornell University is located in New York City and is part of a complex of adjoining world-renowned institutions on Manhattan's East Side. It is dedicated to excellence in biomedical research. The school's location in New York City is an exciting and safe place to live, and our residential buildings are modern and inexpensive. Training toward the Ph.D., M.S. and combined M.D.-Ph.D. degrees is offered by members of the basic and clinical units of Cornell's Medical College and the Sloan-Kettering Institute. With a roster of 220 outstanding faculty members and 240 students, the school offers a faculty-to-student ratio that ensures a close and productive working relationship between each student and their faculty mentor.

We invite you to examine the programs defined in this catalog. We are happy to receive your application for admission should you decide that your own scientific interests and preparation match with the graduate training offered by our institution.

It is our intention to ensure that you are among the vanguard of successful, competent scientists in any program of study by the time you complete your training at our institution.

David P. Hajjar, Ph.D.
*The Frank H. T. Rhodes Distinguished Professor and Dean*

# Weill Graduate School of Medical Sciences of Cornell University

## Organization

Members of the professional staffs of two major medical institutions—Weill Medical College of Cornell University (WMCCU) and the Sloan-Kettering Institute (SKI), the basic research arm of Memorial Sloan-Kettering Cancer Center—form the core faculty of the Graduate School of Medical Sciences. This unique academic partnership was formalized in 1952 under the auspices of the Graduate School of Cornell University at Ithaca and has resulted in the creation of a faculty whose research interests span the full spectrum of biomedicine. This well-integrated faculty has had one unifying mission – to offer a carefully designed, research-oriented graduate program that adheres to the highest standards of graduate education.

The Weill Graduate School of Medical Sciences of Cornell University is part of a large biomedical center extending along York Avenue between 65th and 72nd Streets on Manhattan's Upper East Side. The center's institutions, which are committed to research training and patient care, include the Weill Medical College of Cornell University, The New York Hospital, the Memorial Sloan-Kettering Cancer Center, The Hospital for Special Surgery, and The Rockefeller University. The great majority of the research laboratories of the faculty of the Graduate School of Medical Sciences and other academic core facilities are located within the Weill Medical College of Cornell University-New York Hospital complex and the research laboratory buildings of the Sloan-Kettering Institute.

Among the many information resources available to students on campus, the Samuel J. Wood Library and C.V Starr Biomedical Information Center are especially noteworthy. The modern library houses over 151,160 volumes and subscribes to 1,424 journals in an ambiance characterized by both beauty and comfort. The library is one of the country's first fully automated medical libraries featuring computer terminals that provide access to its collections from any of several hundred networked desktop computers and student workstations throughout the Medical Center. In addition, the Nathan Cummings Center at Memorial Sloan-Kettering Cancer Center has joined with the libraries of the Weill Medical College of Cornell University, The Hospital for Special Surgery, and The Rockefeller University to share databases.

There are a wide variety of training opportunities in biomedical science available to graduate students at the Graduate School. More than 220 faculty members with common interests in graduate education and basic biological and biomedical scientific research become members of the graduate school faculty in a particular Program of Study headed by two Program Chairpersons and a Program Director. The Graduate School of Medical Sciences offers Ph.D. training in the following 7 programs:

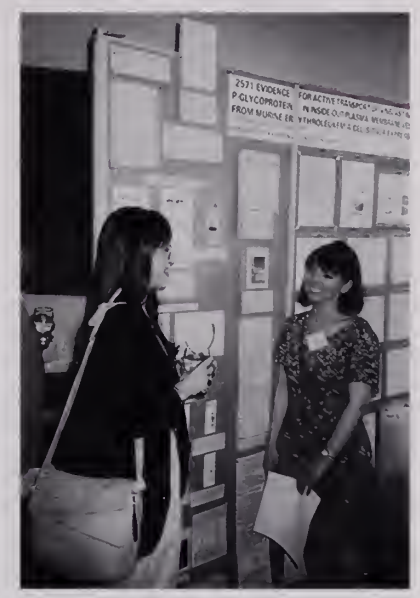
- **Biochemistry & Structural Biology**
- **Cell Biology & Genetics**
- **Immunology**
- **Molecular Biology**
- **Neuroscience**
- **Pharmacology**
- **Physiology, Biophysics, & Molecular Medicine.**

In addition, the Graduate School of Medical Sciences also offers a Master of Science Degree from the program in:

- **Clinical Epidemiology and Health Services Research**

to qualified physicians and nurses with relevant experience.

## Student Training



All students admitted to the Graduate School of Medical Sciences are provided a generous stipend of $22,000 per year for living expenses in addition to a full fellowship covering all tuition expenses. Students apply for admission to the Program of Study of their choice. Initial program selection is often guided by a student's prior research experience. However, the initial designation of a program is far from rigid. For example, a student after becoming aware of the great variety of research projects available for thesis preparation, may remain in their original program but may choose a faculty member affiliated with another program as thesis advisor. Students may also change programs altogether.

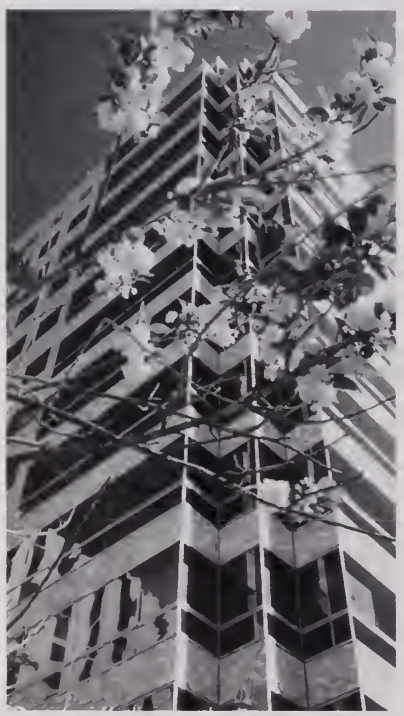
Entering students take a series of intensive courses required by the Program of Study which are intended to give a deep fundamental understanding of the discipline and provide an introduction to research at the frontiers of these research areas. First year students also perform 12 week rotations in laboratories of the faculty, allowing them to do research in a variety of disciplines that will aid them in the selection of a thesis project. These rotations make the student aware of the intellectual breadth and depth of research conducted by the faculty and how modern research is conducted using sophisticated state-of-the art methodologies.

In addition to conducting experimental laboratory research, students learn to communicate their work to other students and faculty by a variety of presentations, such as the Vincent duVigneaud Memorial Research Symposium organized by graduate students and held annually on campus. Students also present their research to other members of their program and at national and international meetings. Students presenting their work at national meetings are offered travel and accommodation funds for scientific meetings during their graduate careers.

Selection of elective course work, as well as thesis research and preparation, are done by the student with the guidance of a Special Thesis Committee of three graduate school faculty members. One of the members of this committee is the student's major sponsor, an individual who serves as research mentor and collaborator for the Ph.D. thesis project.

By the end of the second year, when the student has completed course work and laboratory rotations, members of the Special Committee and two other selected faculty members administer the written and oral Admission to Doctoral Candidacy Examination (ACE). The aim of this examination is to allow the student to demonstrate his or her general knowledge in a chosen area of specialization, as well as demonstrate an ability to approach experimental design with creativity and technical insight. It is the responsibility of the Special Committee to recommend the award of the Ph.D. degree. This recommendation requires not only the fulfillment of certain formal academic requirements, but is also based on evidence of the development by the candidate of a critical and creative approach to science. The demonstration of this ability is embodied in the doctoral thesis which the candidate presents to the faculty as an original research contribution.

All students in the Graduate School are in training for the Ph.D. degree. A small number of college graduates are admitted each year to the Tri-Institutional M.D.-Ph.D. Program. The admissions process for the M.D./Ph.D. Tri-Institutional Program is completely independent of applications to either the Weill Graduate School of Medical Sciences of Cornell University or the Weill Medical College of Cornell University. Those individuals contemplating a dual M.D./Ph.D. career are encouraged to apply to the Tri-Institutional M.D./Ph.D. office on campus (E-mail: mdphd@mail.med.cornell.edu).



## Student Life

The Weill Graduate School of Medical Sciences of Cornell University offers apartment housing to all full-time students for the Ph.D. training period. Rents paid by students are considerably lower than those charged for comparable housing on Manhattan's Upper East Side. Rents charged are very affordable in relation to stipend support awarded to each student, leaving a reasonable amount for comfortable living in Manhattan.

Students live within a few blocks of classrooms and laboratories, on a self-contained campus that is part of a safe residential neighborhood on the prestigious Upper East Side of Manhattan. Numerous shops and restaurants in the immediate vicinity lend this neighborhood an aura of a small, well-defined community.

Student life is dramatically augmented by being located within one of the world's great cities – a metropolis that Cornell students enjoy soon after their arrival on campus when they are taken on tour as part of their orientation program. New York City offers an unmatched range of cultural and recreational activities, many within walking distance of the campus, and all readily accessible by public transport. Much of the world's best art, music, theater, ballet, cinema, and cuisine is concentrated on Manhattan island, at every student's doorstep. Our major museums are world-famous, ranging from the Museum of Modern Art, the Whitney Museum of American Art, the Metropolitan Museum of Art, and the Guggenheim Museum, all within walking distance of the campus. West of this area, across Central Park, are the American Museum of Natural History (with its famous dinosaur exhibit) and the Lincoln Center for the Performing Arts, featuring the

Metropolitan Opera and the New York Philharmonic. Farther downtown, Carnegie Hall, renowned for its offerings of both classical music and jazz, is located amidst New York's most fashionable shops. On summer evenings, free concerts and opera are performed on the lawns of Central Park. Many of the cultural events, including Broadway plays, movies, operas, and concerts, are provided to graduate students at ticket prices subsidized by the Graduate School.

For sports enthusiasts, there is Madison Square Garden, home to the Knicks and Rangers. Magnificent Central Park and the East River Promenade are nearby for strolling, biking, jogging, and roller blading. Subsidized admissions to a complete workout gymnasium, including a swimming pool, are available through the Graduate School. During the warmer months, street fairs are held in various neighborhoods of the city.

Immediately surrounding the campus, our students' non-academic needs are met in a variety of ways. Free noon-time music recitals, featuring fine soloists and groups, are held on Fridays on the adjacent Rockefeller University campus. Students also participate in jogging, aerobics, weightlifting, basketball, and squash on campus. Numerous international restaurants and first-run cinemas provide nourishment and entertainment for every taste. For food shopping, there are several supermarkets, and a small grocery or take-out deli on nearly every street corner.

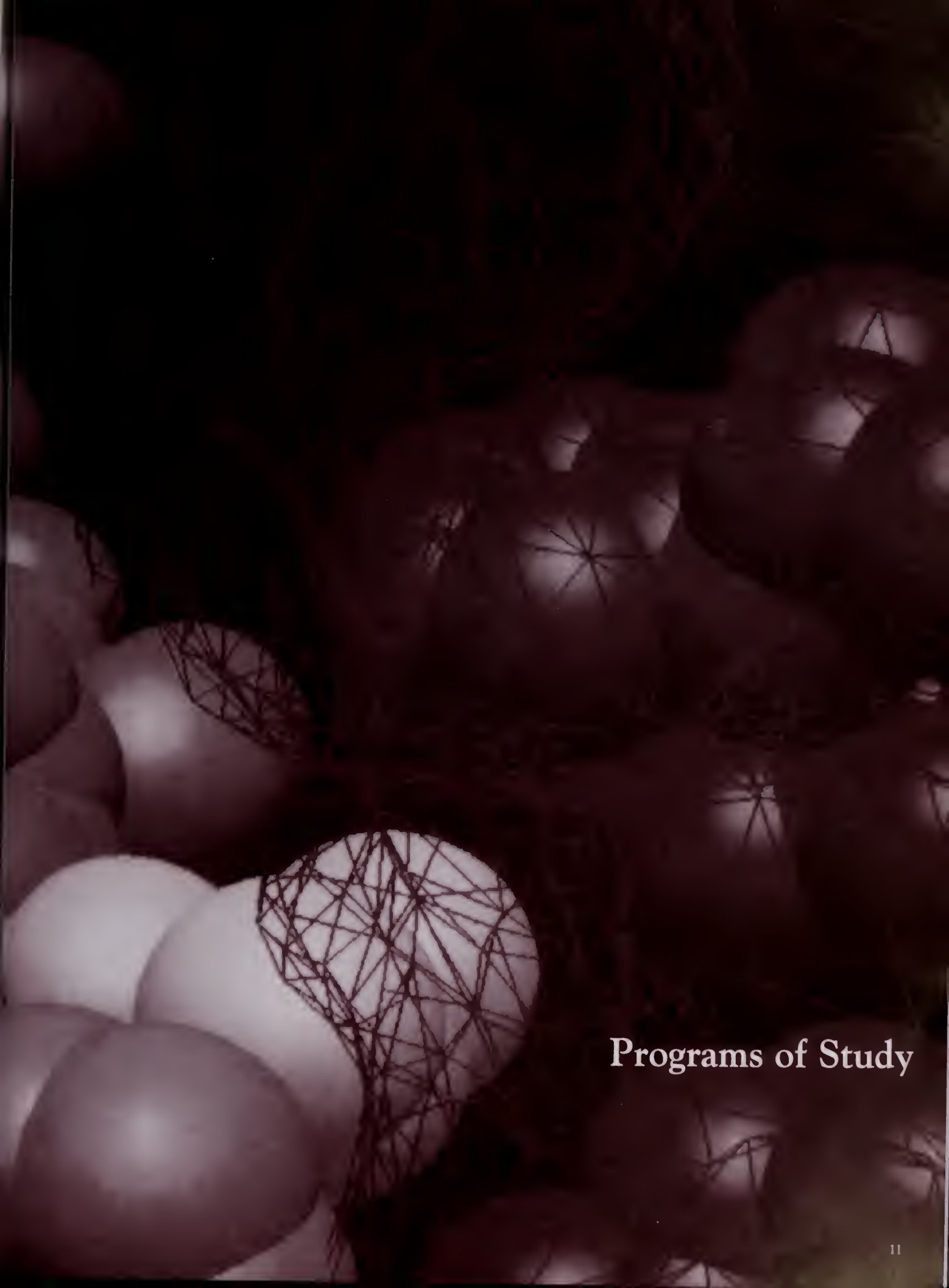
Those inclined to roam a short distance beyond New York City can participate in student-organized hiking or skiing trips to the mountains north of the city. Also within easy reach, Long Island is surrounded by beautiful beaches facing the Atlantic Ocean.

New York City is an unparalleled place to learn and to do science. Further excitement and enrichment are in store for the student who comes here.

## Training Grant Support Available for Pre-Doctoral Students

In addition to the central fellowships that are available to support our pre-doctoral students, a number of graduate students are also supported by training grants from the National Institutes of Health (NIH), the Lucille P. Markey Charitable Trust, and the Cancer Research Institute.

| PROGRAM DIRECTOR | TITLE | AGENCY |
|---|---|---|
| Donald Fischman | Training Program in Molecular and Cellular Biology | National Institute of General Medical Sciences |
| Marvin Gershengorn | Training Program in Molecular Medicine | Lucille P. Markey Charitable Trusts |
| Lorraine Gudas | Cancer Pharmacology | National Cancer Institute |
| David Hajjar | Vascular Biochemistry and Atherosclerosis | National Heart, Lung, and Blood Institute |
| Charles Inturrisi | Pharmacology and Neuroscience of Drug Abuse | National Institute on Drug Abuse |
| Enrique Rodriguez-Boulan | Tri-Institutional Training Program in Vision Research | National Eye Institute |
| John Wagner | Molecular Mechanisms of Neurological Disease | National Institute of Neurological Disorders and Stroke |
| Carl Nathan | Pre-Doctoral Fellowship Program in Tumor Immunology | Cancer Research Institute |



# Programs of Study

# Biochemistry & Structural Biology Program

## FACULTY

Olaf S. Andersen
Francis Barany
Esther M. Breslow
Jonathan Goldberg
Steven S. Gross
David P. Hajjar
Jerard Hurwitz
Richard N. Kolesnick
Harry M. Lander
Christopher Lima
Min Lu
Kenneth J. Marians
Frederick R. Maxfield
Timothy E. McGraw
Dimitar B. Nikolov
Dinshaw J. Patel
Nikola P. Pavletich
Marilyn D. Resh
Hugh D. Robertson
Michael K. Rosen
James E. Rothman
Timothy Ryan
Stewart Shuman
Suresh S. Tate
Paul Tempst
Jon S. Thorson
Hao Wu

### Graduate Program Chairpersons

Frederick R. Maxfield, Department of Biochemistry, Weill Medical College of Cornell University, Room E219, 1300 York Avenue, New York, NY 10021, (212) 746-6405.

Dinshaw J. Patel, Cellular Biochemistry & Biophysics Program, Sloan-Kettering Institute, 1275 York Avenue, New York, NY 10021, (212) 639-7207.

### Graduate Program Director

Timothy E. McGraw, Department of Biochemistry, Weill Medical College of Cornell University, Room E215, 1300 York Avenue, New York, NY 10021, (212) 746-6405, E-mail: temcgraw@mail.med.cornell.edu.

**Calmodulin-dependent Protein Kinase**
*(Goldberg/Kuriyan)*

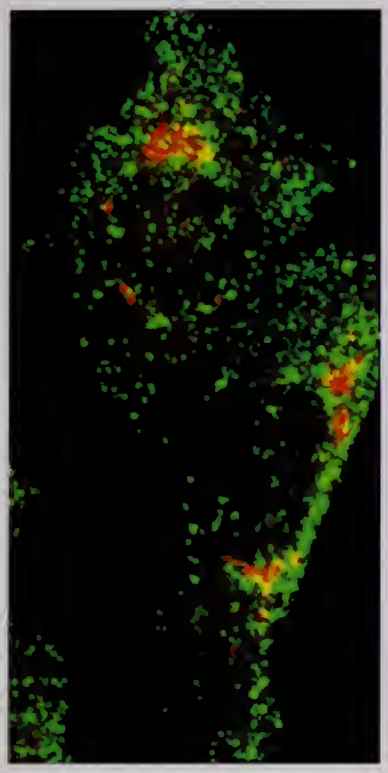
## OVERVIEW OF RESEARCH ACTIVITIES

The Program in Biochemistry & Structural Biology offers unique opportunities to develop comprehensive research training in areas of: 1) molecular structure determination, 2) molecular mechanism of membrane trafficking, 3) protein folding, 4) signal transduction mechanisms, and 5) gene structure and nucleic acid chemistry. All research laboratories are taking a biochemical or biophysical approach to the study of biological systems.

Molecular structure determination is studied at different levels by investigators in the Program. ***Olaf Andersen*** uses molecular modeling systems coupled with single-channel experiments to define the structure of ion conducting channels. ***Jonathan Goldberg*** uses x-ray crystallography to study protein and lipid kinases involved in signal transduction. ***Dimitar Nikolov*** also uses x-ray crystallography to study signal transduction elements of the nervous system, such as axon guidance molecules. The structures of oncogenes and tumor suppressors are analyzed via x-ray crystallography by ***Nikola Pavletich:*** NMR is used by ***Michael Rosen*** to determine the mechanisms by which GTP-binding proteins interact with other proteins. NMR approaches and studies of molecular dynamics are used by ***Dinshaw Patel*** to determine solution structures of nucleic acids.

The molecular mechanism of membrane trafficking are studied by several investigators. ***Frederick Maxfield's*** laboratory uses optical microscopy to observe and understand receptor trafficking and cell motility. ***Tim McGraw*** uses molecular cell biological methods to study general endocytic membrane recycling and insulin-regulated membrane trafficking. ***Tim Ryan*** uses quantitative optical methods to study synaptic vesicle recycling. ***James Rothman*** studies intracellular vesicle traffic and protein folding in an attempt to understand how cells distribute newly synthesized proteins.

Protein folding and translocation are studied by several investigators. ***Esther Breslow*** is currently studying how the structure of a pituitary protein, neurophysin, relates to oxytocin and vasopressin binding and function. ***Min Lu*** uses biophysical and molecular biological methods to study the structure and function of the HIV viral envelope glycoprotein. ***Suresh Tate*** investigates the molecular basis of mammalian amino acid transport.



***Different endocytic compartments in a cell.*** *Two different endocytic compartments are shown in the two cells in this fluorescence color image which was obtained by confocal microscopy. The endocytic recycling compartment, shown in red, is identified by a protein that it contains, fluorescent transferrin. This compartment has a compact morphology near the cell nucleus. The late endosome has a more dispersed punctate appearance, and is identified by a green fluorescent antibody against one of its resident proteins, the mannose-6-phosphate receptor. The lack of overlap between the two colors demonstrates that these proteins are in distinct, separate intracellular compartments. (Maxfield Laboratory)*

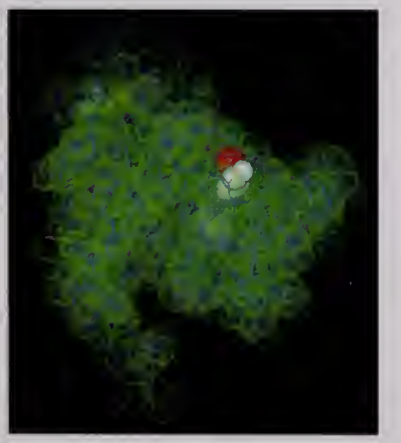


*Image of single Cys residue in p21ras that is modified by nitric oxide and triggers activation. (Lander Laboratory)*

Signal transduction processes are studied by several laboratories. ***Christopher Lima*** studies the structure and function of novel phosphotransferases. ***Hao Wu*** is studying the structural mechanisms of receptor signal transduction for the TNF family of receptors in cell survival and cell death using x-ray crystallography. ***Steven Gross*** is undertaking molecular studies to define nitric oxide biosynthesis and its physiological action. ***David Hajjar's*** laboratory is determining the structure-function relationship between lipoproteins and their receptors, and their impact on cholesterol trafficking. ***Richard Kolesnick*** examines how sphingomyelin and ceramide participates in signaling which can impact on apoptosis in the cell. Identification of the signaling elements and structures required for free radical signal transduction is examined by ***Harry Lander's*** laboratory. ***Marilyn Resh's*** laboratory focuses on the role of fatty acid acylation processes in the determination of the structure and functioning of signal transducing proteins.

DNA replication is studied by several investigators in the Program. ***Jerard Hurwitz's*** laboratory studies DNA replication of SV40 DNA and DNA replication within eukaryotic cells. ***Kenneth Marians*** uses purified proteins to determine the enzymatic mechanisms required for DNA replication and the role of topoisomerases in this process. ***Stewart Shuman's*** laboratory examines transcription termination processes and topoisomerase function.

Nucleic acid and organic chemistry are also actively investigated in the Program. ***Francis Barany*** studies protein-DNA interactions and uses protein engineering to study cancer. ***Hugh Robertson*** examines the structure and function of biologically-active RNA molecules. ***Paul Tempst*** develops methods for ultra-microsequencing of proteins. ***Jon Thorson*** investigates the enzyme catalysts in biosynthetic pathways and his laboratory is focusing on the functional domains of antitumor antibiotics.

More complete information can be found under Faculty Research Descriptions.

## PROGRAM REQUIREMENTS

**Admissions:** The Biochemistry & Structural Biology Program offers training that emphasizes the chemistry of life processes and the relationship between biomolecular structures and their functional properties. Program admission requires a background in general, organic, and physical chemistry and general biology, as well as evidence of comprehension of modern experimental physics and mathematics. Additional preparation in undergraduate biochemistry and cell biology is preferred. Students may remedy deficiencies in these areas during the summer before entering graduate school, or in special cases, during the first year of graduate study.

The Graduate Record Examination (including the advanced test in chemistry or biochemistry) is required. Applicants from abroad are also required to take the TOEFL examination.

**Course of Study:** Within the framework of degree requirements and in consultation with the student, the course of study is planned to fit the need of the individual. The curriculum is designed to provide a broad, general background in graduate biochemistry, molecular biology, and cell biology that is tailored to the needs and interests of each student.

Students entering the Biochemistry & Structural Biology Program are *required* to take the following courses:

1. Biochemistry & Structural Biology
2. Cell Biology
3. Molecular Genetics
4. Biochemistry & Structural Biology Journal Club.

In addition, students must also select *four other elective courses, at least two of which must come from the following selections:*

1. Protein-Nucleic Acid Interactions
2. RNA World

3. Structural Analysis
4. Membrane Biology.

Beyond these general course requirements, students are strongly encouraged to take additional courses offered by the Program or by others in the Graduate School that will strengthen their preparation for research.

**Laboratory Rotations:** Entering graduate students must also rotate among three laboratories of faculty of their choice for three-month periods, allowing them to become familiar with the ongoing research activities of the Program, and aiding in their selection of a thesis project. It is expected that all students will choose a thesis laboratory following completion of their laboratory rotations.

**Admission to Doctoral Candidacy Examination and Research Supervision:** Upon choosing a thesis laboratory, a Special Committee will be constituted, which consists of the thesis mentor (known as a major sponsor) and two minor sponsors. There are two parts to the written portion of the exam. One part is a research proposal (NIH format) written by the student in an area unrelated to the thesis project. In addition, a short (2-3 page) thesis research proposal, stating the aims of the thesis project is required. This examination, normally given at the end of the student's second year, is designed to test the student's general proficiency in Biochemistry & Structural Biology. It contains both written and oral components and places emphasis on the student's ability to critically analyze and design appropriate approaches to solve various scientific problems. The student will not be formally admitted to Ph.D. degree candidacy until he or she has successfully passed The Admission to Doctoral Candidacy Examination.

Finally, completion of the Ph.D. in Biochemistry & Structural Biology requires an original thesis based on the student's research and a thesis defense.

# Cell Biology & Genetics Program

## FACULTY

Rosemary F. Bachvarova
Craig T. Basson
Robert Benezra
Carl P. Blobel
Adele L. Boskey
Patrick J. Brennwald
Anthony M.C. Brown
Michael Caudy
Ethel Cesarman
Raju S.K. Chaganti
Nathan Ellis
Donald A. Fischman
Robert P. Fisher
Leonard P. Freedman
James L. German, III
Marvin C. Gershengorn
Filippo G. Giancotti
Barry M. Gumbiner
Katherine A. Hajjar
Maria Jasin
Irwin Klein
Eseng Lai
Lucio Luzzatto
Paul A. Marks
Joan Massagué
Takashi Mikawa
Malcolm A. S. Moore
Ralph L. Nachman
Carl F. Nathan
Joel D. Pardee
Marilyn D. Resh
Richard A. Rifkind
Hugh D. Robertson
Enriqué Rodriguez-Boulan
Neal Rosen
James E. Rothman
Urs Rutishauser
Roy L. Silverstein
Thomas H. Söllner
Lisa Staiano-Coico
Ching-Hwa Sung
John A. Wagner
Martin Wiedmann
Paul Wilson
David Zakim

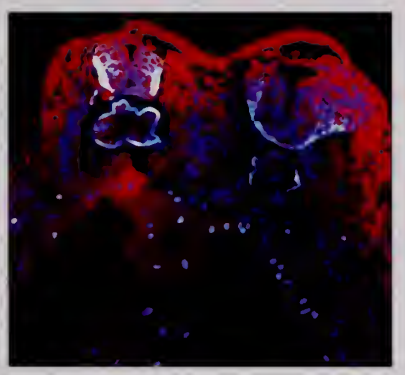
### Graduate Program Chairpersons

Joan Massagué, Cell Biology Program, Sloan-Kettering Institute, 1275 York Avenue, New York, NY 10021, (212) 639-8975.

Carl F. Nathan, Department of Cell Biology & Anatomy, Weill Medical College of Cornell University, 1300 York Avenue, New York, NY 10021, (212) 746-2985.

### Graduate Program Director

Leonard P. Freedman, Cell Biology Program, Sloan-Kettering Institute, Box 470, 1275 York Avenue, New York, NY 10021, (212) 639-2976, E-mail: l-freedman@ski.mskcc.org.



*Section through a xenopus embryo showing duplication of the spinal column by injection of beta-catenin mRNA (Gumbiner Laboratory)*

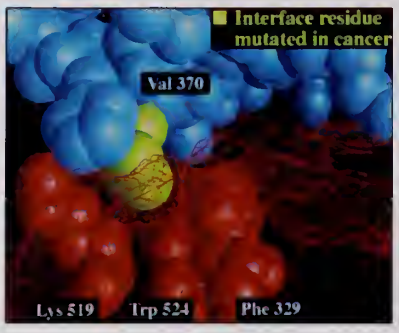
## OVERVIEW OF RESEARCH ACTIVITIES

The research interests of the Cell Biology & Genetics Graduate Faculty comprise a wide range of topics related to the control of normal and malignant cell growth and differentiation. Purified proteins, isolated cells and tissues, and whole organisms are all being exploited as model systems. A variety of molecular, cellular, and genetic techniques are being used to address the following questions: How is gene expression regulated? How are proteins folded and targeted to specific locations within the cell? How do cells interact and how does this influence tissue function? How is the growth of normal and transformed cells regulated at the biochemical and genetic level?

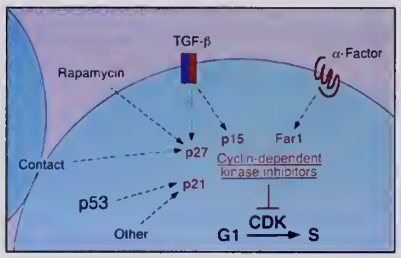
Control of gene expression by helix-loop-helix proteins is being studied at the molecular level by ***Robert Benezra,*** who is interested in regulation of differentiation, and ***Michael Caudy,*** who is studying Drosophila neurogenesis. ***Leonard Freedman*** focuses on transcriptional control by nuclear hormone receptors, while ***Irwin Klein's*** laboratory is interested in cardiac gene expression.

The precise expression of tissue-specific proteins is critical for coordination of development and differentiation. ***Rosemary Bachvarova*** is studying the process of gastrulation in embryos. Several faculty members are studying the molecular aspects of tissue formation, including muscle development ***(Donald Fischman),*** heart and brain differentiation ***(Takashi Mikawa),*** brain and kidney development ***(Eseng Lai),*** and epithelial differentiation ***(Lisa Staiano-Coico). Paul Wilson*** is studying the morphogenesis of the dorsal mesoderm and neural fates during frog (xenopus) development.

The biochemistry of human tissue function is of great interest to many laboratories. ***Adele Boskey*** is investigating biologic calcification, while ***Ching-Hwa Sung*** focuses on




*A loss of pathways that inhibit cell division can contribute to cancer. TGF-β signal transduction, which is being elucidated by Dr. Joan Massagué and his group, is one such pathway. The Smad proteins are a newly discovered family of factors that carry the TGF-β signal from membrane receptors to the nucleus. The X-ray crystal structure of Smad proteins resolved by Drs. Nikola Pavletich and Yigong Shi has revealed how mutations found in tumors of the pancreas and colon disrupt the ability of these proteins to interact with each other and to carry on the growth inhibitory function.*




***CDKs and CDK inhibitors.*** *Cyclin-dependent kinases (CDKs) play a central role in allowing progression through the cell cycle. Their activity is suppressed by CDK inhibitors. Many inhibitory signals, such as those initiated by TGFβ and contact in mammalian cells, by alpha mating factor in yeast, or by antiprolifiration drugs such as rapamycin, arrest the cell cycle through CDK inhibitors. Many investigators in the Program are studying these pathways in normal and tumor cells. (Fisher, Freedman, Koff, Hurwitz, Massagué, Pavletich, Rosen Laboratories)*

rod outer segment biology. Specific signaling pathways activated in endothelial cells ***(Katherine Hajjar)***, platelets ***(Ralph Nachman)***, and phagocytes ***(Carl Nathan)*** are being elucidated in an effort to understand the roles of these cells in human diseases.

The biosynthesis and targeting of proteins to specific subcellular locations is being addressed using biochemical and cytological techniques. ***Martin Wiedmann*** studies polypeptide chain synthesis on the ribosome. The laboratories of ***James Rothman, Patrick Brennwald,*** and ***Enriqué Rodriguez-Boulan*** are all involved in molecular and biochemical aspects of intracellular protein trafficking using cell-free systems ***(James Rothman)***, yeast ***(Patrick Brennwald)***, or polarized cells ***(Enriqué Rodriguez-Boulan)***. Once proteins are targeted to specific locations, their ability to mediate cell-cell interactions at the membrane is precisely controlled. Cellular adhesion by cadherins and catenins ***(Barry Gumbiner)*** and the monocyte protein CD36 ***(Roy Silverstein)*** as well as signaling by cell-surface integrins ***(Carl Blobel, Filippo Giancotti)*** are major research interests. In addition, ***Joel Pardee*** studies actin cytoskeleton interactions, whereas ***David Zakim*** examines protein binding to lipid bilayers.

Control of normal and malignant cell growth by oncogenes, growth factors, and the cell cycle are major research themes in the Cell Biology & Genetics Program. The laboratories of ***Paul Marks*** and ***Richard Rifkind*** study growth and differentiation of erythroleukemic cells. ***Anthony Brown*** is interested in signaling by the Wnt family of oncoproteins, ***Neal Rosen*** is examining the role of tyrosine kinases in human breast and colorectal cancer, and ***Marilyn Resh*** studies the mechanisms of membrane binding and signaling by viral and cellular oncoproteins. The molecular mechanism of growth factor and receptor action is of interest to several laboratories, including neuronal growth factors ***(John Wagner)***, colony stimulating factors ***(Malcolm Moore)***, TGFβ ***(Joan Massagué)*** and G protein coupled receptors ***(Marvin Gershengorn)***. Cell cycle control is a major thrust of the laboratory of ***Robert Fisher*** and interfaces with the growth control mechanisms studies by several other faculty members ***(Marks, Rifkind, Rosen, Massagué)***.

Human genetic abnormalities at the chromosomal level are being studied with the goal of designing effective therapies to treat human diseases. ***Raju Chaganti*** uses cytogenic methods to identify genetic alterations in human tumors. ***James German's*** laboratory analyzes defects in Bloom's syndrome, while ***Lucio Luzzatto*** is interested in paroxysmal nocturnal hemoglobinuria as well as G6PD deficiency. ***Maria Jasin*** is developing gene targeting methodology to target chromosomal breaks, while ***Hugh Robertson*** is exploiting ribozymes to cleave harmful RNAs.

More complete information can be found under Faculty Research Descriptions.

## PROGRAM REQUIREMENTS

**Admissions:** The Program in the Cell Biology & Genetics offers advanced study leading to the Ph.D. degree. The program is intended to prepare students for a career in basic research and teaching in cell or developmental biology, genetics, molecular biology, or related disciplines. Students with a strong background in genetics, cell, molecular, or developmental biology are urged to apply.

The Graduate Record Examination (including the advanced test in biology, chemistry, biochemistry, or cell and molecular biology) is required. Applicants from abroad are, in addition, required to take the TOEFL examination.

**Joint Curriculum:** The Cell Biology & Genetics and Molecular Biology Graduate Programs offer a joint curriculum in Cellular, Molecular, and Developmental Biology. Students entering both programs will have the same course, laboratory rotation, and first year exam requirements, as well as the same Admission to Doctoral Candidacy Exam (ACE). These requirements are outlined below. Program affiliation will be determined by the choice of thesis laboratory, usually by the beginning of the second year.

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**Joint Program Retreat:** Students have numerous opportunities to meet with the faculty, including faculty talks during the first year and a retreat held at a resort outside the New York City area, where faculty and students present and discuss their work.

# Immunology Program

## FACULTY

Leif Bergsagel
Paolo Casali
Ethel Cesarman
Selina Chen-Kiang
Mary K. Crow
Lisa R. Denzin
Bo Dupont
Keith B. Elkon
Ulrich Hammerling
Alan N. Houghton
Lionel B. Ivashkiv
Hsiou-Chi Liou
Kenneth O. Lloyd
William A. Muller
Henry W. Murray
Carl Nathan
Janko Nikolic-Zugic
Richard J. O'Reilly
Howard T. Petrie
David N. Posnett
Carlo Russo
Michel Sadelain
Jane E. Salmon
Derek B. Sant'Angelo
Elaine Schattner
Kendall A. Smith
Marc E. Weksler

### Graduate Program Chairpersons

Alan N. Houghton, M.D., Immunology Program, Sloan-Kettering Institute, Room K-718, 1275 York Avenue, New York, NY 10021, (212) 639-7106.

Kendall A. Smith, M.D., Department of Medicine, Weill Medical College of Cornell University, 1300 York Avenue, Room LC-907, New York, NY 10021, (212) 746-4464.

### Graduate Program Director

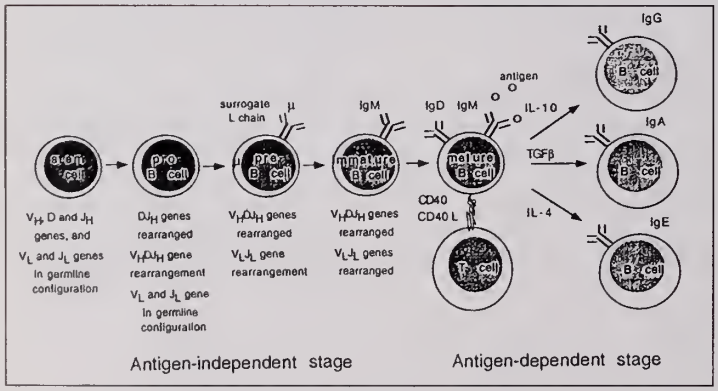
Paolo Casali, M.D., Division of Molecular Immunology, Department of Pathology, Weill Medical College of Cornell University, 1300 York Avenue, Room C-312, New York, NY 10021, (212) 746-6452.

Program information E-Mail: crespot@mskcc.org.

## OVERVIEW OF RESEARCH ACTIVITIES

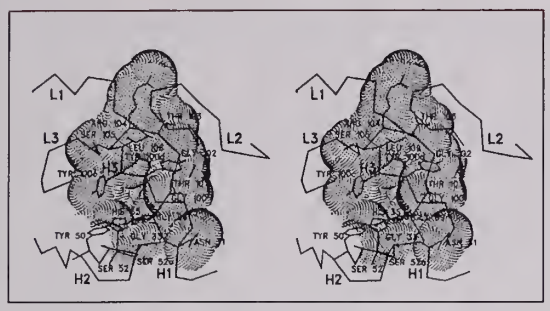
The Immune System is made up of specialized cells, tissues, and molecules. Research in the Immunology Program is applied to understand the basic mechanisms of development and function of this system in health and disease.

Understanding how the specialized cells of the immune system develop is central to understanding how the repertoire of the immune system is generated and how self reactivity is avoided. T lymphocytes play a primary role in the regulation of the immune system. Their precursors leave the bone marrow to mature in the thymus. ***Janko Nikolic-Zugic*** studies the role of MHC and TCR in thymic T cell selection, and ***Derek Sant'Angelo*** studies how T lymphocytes are negatively and positively selected during development and differentiation. ***Howard Petrie*** examines how T cells make decisions about life and death during development. B lymphocytes develop in the bone marrow, and then go on to colonize the peripheral lymphoid organs. The products of these cells, antibodies, and their regulation are the focus of ***Paolo Casali's*** research. Finally, ***Lisa Denzin*** investigates how antigens are processed and presented to the immune system.




*B cell Ontogeny*
*(Casali Laboratory)*

All of the cells in the immune system are regulated by soluble molecules called cytokines. ***Kendall Smith*** focuses on the role of IL-2 in activation and proliferation of lymphocytes and natural killer (NK) cells. Cytokines as well as cell surface molecules affect the function through highly specialized signal transduction pathways. ***Lionel Ivashkiv*** studies the Jak-STAT




*A model of the antibody-binding site of R24 monoclonal antibody derived from the crystal structure of R24 F(ab) 2 fragments. The R24 antibody binds to the ganglioside GD3. R24 is used to treat patients with cancer. (Houghton Laboratory)*

signaling pathway in inflammatory diseases. The primary objective of ***Hsiou-Chi Liou's*** research is to understand the role of the components of the NF-κB proteins in signaling lymphocyte activation and differentiation. The role of IL-6 in the terminal differentiation of B cells is addressed by ***Selina Chen-Kiang. Ulrich Hammerling*** studies the role of vitamin A and its metabolites in lymphocyte differentiation and growth control. Co-receptors on T cells such as CD2 and CD28 also signal through specialized pathways which are under investigation by ***Bo Dupont.***

The immune response to infectious agents is of paramount importance to the survival of the host. ***Carl Nathan's*** research is focused on the molecular mechanisms whereby neutrophils and macrophages kill infectious organisms. ***Henry Murray*** studies how T cells and macrophages cooperate to produce cytokines that limit replication of protozoa. ***William Muller*** addresses the biology of adhesion molecules responsible for the binding and emigration of leukocytes across vascular endothelial cells. The immune response to the human immunodeficiency virus (HIV) has become a major medical problem and ***David Posnett's*** research is aimed at elucidating how the T cell responds to HIV in patients with AIDS.

Three major areas of applied immunology are tumor immunology, autoimmunity, and transplantation immunity. ***Alan Houghton*** studies the host immune response to cancer cells and is developing vaccines to immunize the host against cancer cells. ***Kenneth Lloyd*** studies the biochemical synthesis and nature of tumor antigens and has developed monoclonal antibodies reactive against these antigens. ***Elaine Schattner*** addresses the dysregulation of apoptotic mechanisms. ***Lief Bergsagel*** studies the modalities of neoplastic transformation in human plasma cells. The role of human herpesvirus (HHV)-8 in lymphoid transformation is the focus of ***Ethel Cesarman's*** research. ***Keith Elkon*** studies basic mechanisms responsible for autoimmunity with particular emphasis on the regulation of apoptosis. ***Mary K. Crow*** examines the T cell repertoire in autoimmune disease, and, also, T cell ligands that regulate B cell activation and death. Phagocytosis of immune reactants play an important role in the effector phase of autoimmunity and their function is under investigation by ***Jane Salmon. Richard O'Reilly*** studies graft-versus-host disease (GVHD), a complication of bone marrow transplantation, and is developing therapeutic strategies to prevent and treat this disease. ***Michel Sadelain*** is developing gene therapy approaches to GVHD as well as other genetic diseases using retrovirus vectors.

There are considerable changes in the immune system that occur during aging and ***Marc Weksler's*** research examines how T and B cell function wanes with age. ***Carlo Russo*** studies T cell co-stimulatory molecules in aging and also works on strategies to improve the immune response to vaccines in elderly individuals.

More complete information can be found under Faculty Research Descriptions.

## PROGRAM REQUIREMENTS

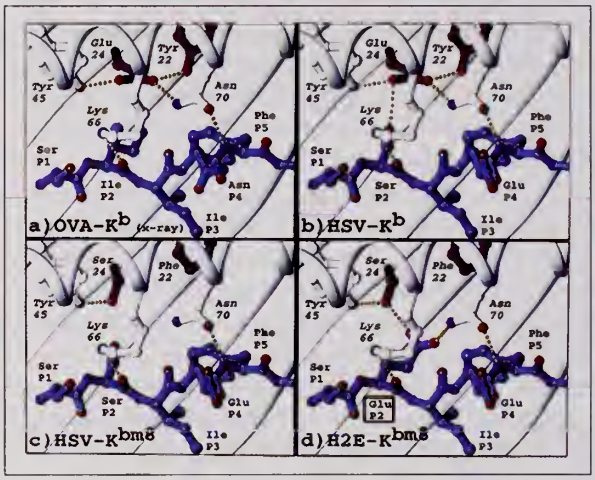
**Admission:** Applicants should have a strong undergraduate background and record of achievement in the biological sciences, including biochemistry, molecular genetics, and microbiology and are also expected to have undergraduate laboratory research experience. An official transcript of the student's undergraduate record is necessary with at least two letters from faculty members who can evaluate the academic potential of the student in a Ph.D. program in Immunology. The application requires a personal statement describing the student's background and specific interest in the Immunology Program. Applicants must submit the results of the Graduate Record Examination, including the advanced test in Biology or Chemistry. Students from abroad are required to take the TOEFL examination.

**Curriculum:** An individual program of didactic study is developed for each student on the basis of the student's interest and prior experience, comprising both required and elective courses.

**Course Requirements:** Students entering the Immunology Program are required to take the following courses.

1. Fundamental Immunology
2. Immunology Graduate Research in Progress
3. Molecular Genetics
4. Cell Biology
5. Biochemistry and Structural Biology
6. Biostatistical Methods
7. Advanced Topics in Immunology, at least 2 modules to be chosen among topics such as: Signal Transduction, B Cells, Apoptosis, Tumor Immunology, Developmental Immunology.

Elective courses may be chosen among all other courses offered by the other Programs of the Graduate School.




*Molecular modelling of the peptide: MHC class I complexes (pictures) and their functional recognition by T cells (not shown) provides new insight into the mechanism of T cell receptor: peptide: MHC interaction.*
*(Nikolic-Zugic Laboratory)*

The Immunology Program offers a series of colloquia on current topics in Immunology with presentations and discussions led by Immunology faculty members. In addition, a wide variety of research seminars by outside speakers are offered throughout the year.

**Laboratory Rotation:** The main focus of the Graduate Program in Immunology is on laboratory research. Each student is required to undertake three rotation projects with different faculty members. The three rotations will be carried out during the third and fourth quarters of the first year and the summer following the first year of study. During the second year, the student is expected to choose a thesis sponsor and to develop a major research proposal for the doctoral thesis.

**Admission to Doctoral Candidacy:** The Admission to Doctoral Candidacy Examination which is ordinarily taken in the spring of the second year, requires both written and oral examination of the candidate's general understanding of Immunology and related subjects.

**Special Committee:** A Special Committee, comprised of the faculty member directly supervising the student's thesis research ("Major Sponsor") and two additional faculty members knowledgeable in the field of study ("Minor Sponsors"), advises the student in his or her research, meeting periodically to monitor progress, and upon completion, to certify the thesis as an official piece of research that satisfies the requirements of the graduate school for the Ph.D. degree. During that time the student will continue to participate in the other educational programs offered by the graduate program but will work full time in the laboratory.

# Molecular Biology Program

## FACULTY

Kathryn Anderson
Francis Barany
Mary Baylies
Peter Besmer
Anthony M. C. Brown
Dale Dorsett
Erik Falck-Pedersen
Lorraine J. Gudas
William K. Holloman
Jerard Hurwitz
Scott Keeney
Andrew Koff
Elizabeth Lacy
Neal Lue
Kenneth J. Marians
Pamela Meluh
Lee Ann Niswander
Mary Ann Osley
Pier Paolo Pandolfi
Mark Ptashne
Beate Schwer
Stewart Shuman
Paul Tempst
Andrew Zelenetz

### Graduate Program Chairpersons

Erik Falck-Pedersen, Department of Microbiology, Weill Medical College of Cornell University, Room B-309, 1300 York Avenue, New York, NY 10021, (212) 746-6505.

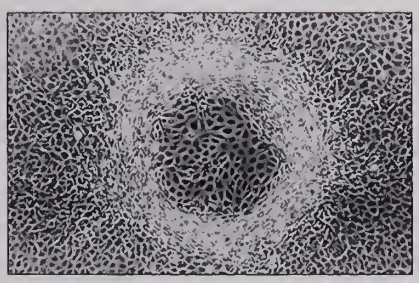
Kenneth J. Marians, Molecular Biology Program, Sloan-Kettering Institute, Room 1117-A, Rockefeller Research Laboratories, 430 East 67th Street, New York, NY 10021, (212) 639-5890.

### Graduate Program Director

Andrew Koff, Molecular Biology Program, Sloan-Kettering Institute, Room 917-D, Rockefeller Research Laboratories, 430 East 67th Street, New York, NY 10021, (212) 639-2354, E-mail: a-koff@ski.mskcc.org.

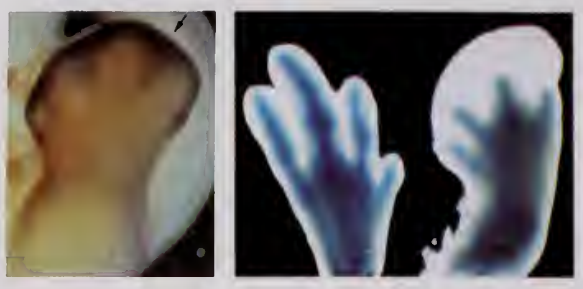
## OVERVIEW OF RESEARCH ACTIVITIES

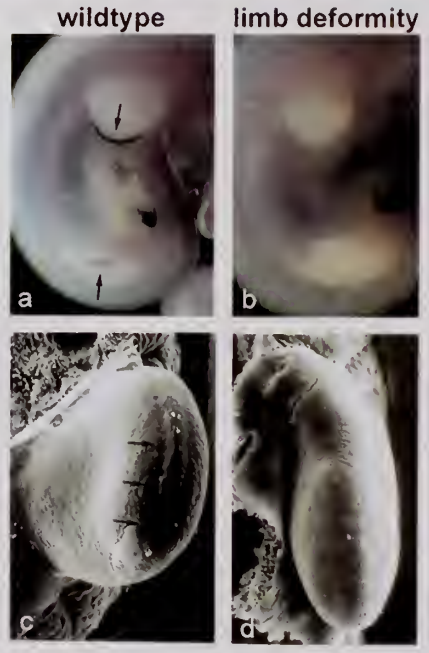
Regulation of cell growth is a shared and unifying research interest to members of the Molecular Biology Graduate Program. The molecular pathways involved in control of cell growth have proven to be remarkably intricate, tying together nearly all the fundamental processes of cellular metabolism. For example, the products of oncogenes, tumor-suppressing, and tumor-enhancing genes have been discovered to participate in pathways as seemingly diverse as signal transduction, repair of damaged DNA, regulation of gene expression, and control of the cell cycle. The research efforts of the faculty of Molecular Biology can be grouped under three broad topics: i) mechanisms of differentiation, growth control, and development, ii) mechanisms of DNA replication, DNA repair, chromosome maintenance, and iii) transcriptional control of gene expression and mRNA biosynthesis.



*A ring of transformed mammary epithelial cells induced by growth of the cells in proximity to a central colony of fibroblasts expressing Wnt-1 protein. (Brown Laboratory)*

Signal transduction is a critical step in the control of cell growth and proper developmental regulation. *Drosophila* is used as a model system to analyze development by ***Kathryn Anderson,*** who studies the manner in which the maternal-effect genes regulate pattern formation in the developing embryo, and ***Mary Baylies,*** who is investigating how the Twist gene product controls cell fate determination in the mesoderm. Another major experimental system for the study of development is the mouse. ***Elizabeth Lacy*** has been isolating genes required for early development, whereas ***Pier Paolo Pandolfi*** has constructed mouse strains inactivated in genes known to be involved in the development of acute promyelocytic leukemia. ***Andrew Koff*** has developed a mouse model system that allows him to study the effect of deregulation of cell cycle control in a complex organism. In a related system, ***Lee Niswander*** studies the interaction of the genes that specify pattern formation in the chick limb. How activated receptor complexes transmit information to control the growth state of a cell is under study by several investigators. ***Peter Besmer*** studies the mechanism of action of the c-kit receptor tyrosine kinase, whereas ***Lorraine Gudas*** is interested in the effects of retinoids on cell growth. ***Anthony Brown*** is elucidating the intracellular signaling pathways by which the Wnt family of proteins act. Often,






*Top Figure* *BMP signaling is required for cell death between the embryonic digits.*
*Left panel illustrates Bmp RNA expression in the interdigital spaces (purple stain marked by arrows).*
*Right panel, right limb: interdigital cells do not die when BMP signaling is blocked by a mutation in the BMP receptor, thus leading to webbing between the digits.*

*Bottom Figure* *The mouse mutation limb deformity causes loss and fusion of bones and digits of the arm and leg. At early stages of limb development, this is manifested by alterations in gene expression as demonstrated by Fgf4 RNA expression (a,b) and by aberrant apical ectodermal ridge formation as illustrated by scanning electron microscopy (c,d).*
*(Niswander Laboratory)*

only very small amounts of proteins involved in these pathways are available for analysis. ***Paul Tempst*** develops methods for ultra-microsequencing of proteins.

The biological mechanisms that mediate chromosome duplication are addressed in a variety of systems ranging from bacteria to humans. ***Kenneth Marians*** is investigating the protein/protein interactions required to make the *E. coli* replisome a super efficient protein machine. ***Jerard Hurwitz*** is defining the proteins required for eukaryotic replication and how they interact with the cell cycle machinery. The molecular basis of DNA recognition by DNA-binding proteins is under study in ***Francis Barany's*** lab. Several laboratories are combining the power of genetics and biochemistry to study aspects of DNA metabolism. The enzymatic machinery involved in repairing damaged DNA is studied in the laboratory of ***William Holloman. Scott Keeney*** is characterizing the genes and mechanisms that are essential to chromosome rearrangement during meiosis, while ***Andrew Zelenetz*** is investigating the mechanisms of cancer-causing DNA translocations in humans. ***Pamela Meluh*** is interested in the biology of the centromere-kinetochore complex involved in chromosome segregation during mitosis, and ***Neal Lue*** is dissecting the enzymatic machinery required for telomere maintenance and replication in yeast.

Basic aspects of gene expression are studied by a number of different investigators. The nature of protein/protein complexes which bind to DNA and act as transcriptional regulators is studied by ***Mark Ptashne. Mary Ann Osley's*** lab uses yeast genetics to unravel the transcriptional activators and repressors that regulate transcription of the histone genes during the cell cycle. In Drosophila and other higher eukaryotes enhancer-dependent, long-range (over 100 kb) regulation of gene expression occurs as part of the developmentally regulated transcriptional control pathways studied in the laboratory of ***Dale Dorsett.*** Using a variety of model systems several laboratories are studying the essential pathways of mRNA processing. ***Stewart Shuman*** investigates the enzymatic mechanisms of transcription initiation, elongation, and termination using yeast and *Vaccinia* virus as a model. ***Beate Schwer*** uses yeast genetics and biochemistry to dissect the biochemistry of mRNA splicing. ***Erik Falck-Pedersen*** uses another eukaryotic virus, *Adenovirus*, as a model to study gene transduction and regulation of mRNA 3'-end formation in mammalian transcription units.

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## PROGRAM REQUIREMENTS

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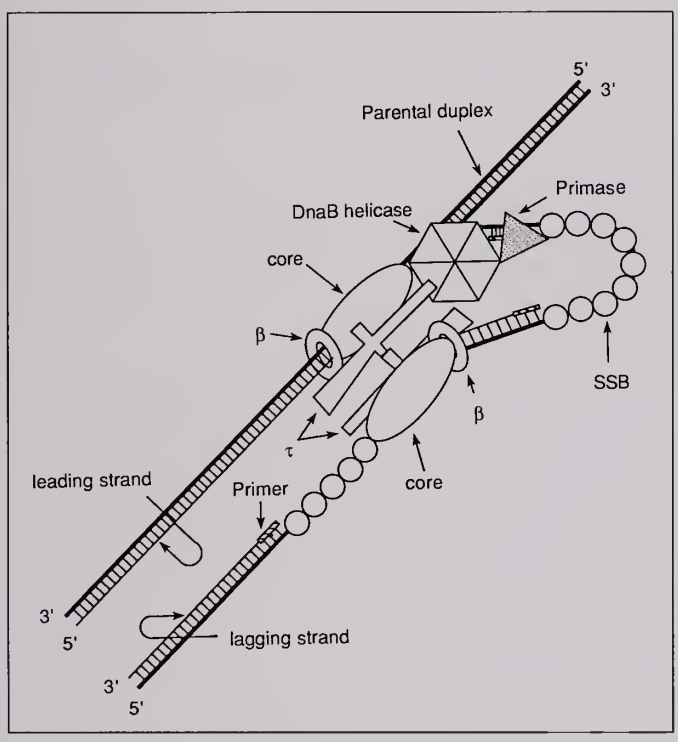


*Protein-protein interactions between the t subunit of the DNA polymerase III holoenzyme and the replication fork helicase, DnaB, defines the leading-strand polymerase. (Marians Laboratory)*

**First year examination:** At the end of the first year, an oral examination is given to each student in order to monitor progress and identify areas of strength and weakness.

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**Joint Program Retreat:** Students have numerous opportunities to meet with the faculty, including faculty talks during the first year and a joint retreat held at a resort outside the New York City area, where faculty and students present and discuss their work.

# Neuroscience Program

## FACULTY

Harriet Baker
M. Flint Beal
Ronald Blasberg
John Blass
Michael Caudy
Arthur Cooper
Robert Duvoisin
Donald Fischman
Henry Furneaux
Daniel Gardner
James Gibbs
Gary Gibson
Eugene V. Golanov
Steven Goldman
Bernice Grafstein
Danielle Greenberg
Barbara Hempstead
Joy Hirsch
Xin-Yun Huang
Charles Inturrisi
Tong Joh
Eseng Lai
Lonny Levin
Teresa Milner
Michiko Okamoto
Gavril Pasternak
Virginia Pickel
Fred Plum
Jerome Posner
Keith Purpura
Donald Reis
Enrique Rodriguez-Boulan
Myrna Rosenfeld
Timothy Ryan
Gerard Smith
Jin Son
Peter Stokes
Ching-Hwa Sung
Miklos Toth
Rosario Trifiletti
Jonathan Victor
Bruce Volpe
John Wagner

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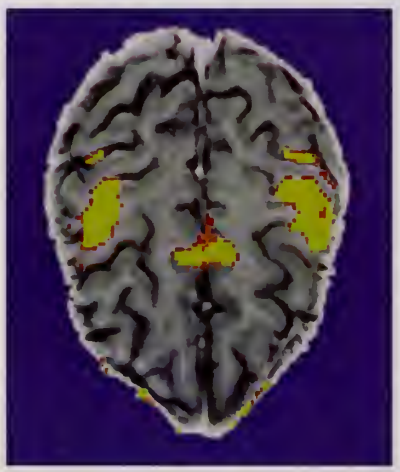
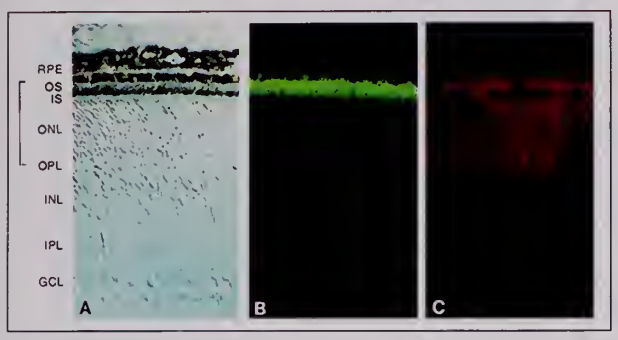


*Functional magnetic resonance imaging reveals regions of the human brain that are neurally active during performance of specific tasks. This figure shows a typical functional brain response when the subject performs a bilateral finger/thumb tapping task. The brain areas that are active (yellow) identify motor (anterior lateral), sensory (posterior lateral), and supplementary motor (medial) areas that participate in these hand movements. This new ability to map brain functions offers many new opportunities to investigate and understand the human brain. (Hirsch Laboratory)*

## OVERVIEW OF RESEARCH ACTIVITIES

The unifying theme of the Program in Neuroscience is a common interest in the development and function of the nervous system. Members of the Program in Neuroscience study the development, structure, and function of the nervous system, using a wide variety of scientific disciplines, including molecular genetics, biochemistry, pharmacology, neuroanatomy, electrophysiology, molecular biology, computational neuroscience, and behavior. They work at the molecular, cellular, and organismal levels, targeting the nervous system in rodents, birds, *Drosophila*, reptiles, and *Aplysia*, as well as in humans. The research interests of the program cover the entire range of neuroscience, including the regulation of neural development, neuronal plasticity, control of neurotransmitter synthesis and release, learning, the response of neurons and neural tissue to injury, the regulation of gene expression, endocrine function, vision and other sensory systems, information processing, and behavior. Many members of the program have a special interest in questions that are particularly relevant to human disease, and their research has important implications for topics such as the regulation of pain, neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, neural tumors, stroke, addiction, and aging. The research interests of the faculty can be grouped into ten major areas including: 1) developmental neurobiology, 2) signaling by neurotransmitters and receptors, 3) the structure of the nervous system and neuroanatomy, 4) signaling by growth factors and molecules in the extracellular matrix, 5) integrative neuroscience, 6) behavior, 7) metabolism and neurotoxicology, 8) vision, and 9) neural disease, with individual faculty frequently having interests in more than one of these areas.




*Double immunofluorescent labeling of wild-type rhodopsin (B) and truncated rhodopsin (C) in transgenic retinas. Note that the truncated rhodopsin is defective in its outer segment (OS) localization in photoreceptors. (Sung Laboratory)*

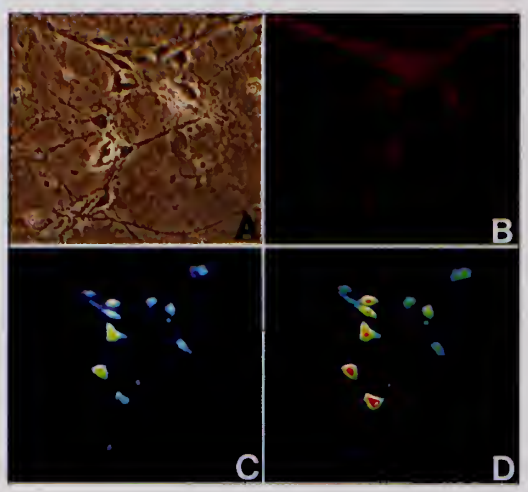
**Developmental Neurobiology.** The development of molecular markers for specific cell types and the isolation of genes that control developmental process have opened new frontiers in developmental neurobiology. ***Harriet Baker*** studies the factors responsible for the maintenance of neural phenotype in the olfactory system and ***John Wagner*** studies the role of peptide growth factors in the visual system. ***Michael Caudy*** studies the role of basic helix-loop-helix proteins in the development of both vertebrate and the *Drosophila* nervous system, while ***Eseng Lai*** studies the role of winged helix transcription factors in the development of the mammalian brain, including the retina. ***Steve Goldman*** has developed methods of studying neurogenesis in the adult vertebrate and the way they migrate into the CNS and form functional connections. ***Jin Son*** is using promoter analysis to determine the factors that control differentiation of specific cell population in the nervous system. ***Henry Furneaux*** studies the role of the Elav-like RNA binding proteins in neuronal differentiation. ***Donald Fischman*** is interested in the development of the neuromuscular junction. ***Tong Joh*** is using neural specific promoters to understand regulated transcription in the nervous system and as tools to understand how inappropriate gene expression can perturb developmental processes. ***Barbara Hempstead*** studies the role of neurotrophin receptors in the development of the neural crest and the retina. ***Bernice Grafstein*** studies axonal transport and regeneration as well as the development of the pia-arachnoid, which helps provide an appropriate environment for neural development.

**Signalling by Neurotransmitters and Receptors.** The study of signaling among neurons and between neurons and other cells lies at the heart of neural functioning, so nearly all laboratories have an interest in this area; several of our faculty, however, focus strongly on the action of neurotransmitters and their receptors. ***Charles Inturrisi*** and ***Gavril Pasternak*** are interested in the neuropharmacology of the opiates and their receptors. ***Xin-Yun Huang*** studies the ways GTP binding proteins and tyrosine phosphorylation are involved in transmitter signaling. ***Robert Duvoisin*** studies glutamate receptors, especially metabatropic glutamate receptors. ***Miklos Toth*** introduces germ-line mutations into serotonin receptors to study their function. ***Timothy Ryan*** uses optical techniques to study the fundamental mechanism of neurotransmitter release. ***Rosario Trifiletti, John Wagner,*** and ***Donald Reis*** all have a special interest in signaling by nitric oxide in the nervous system. ***Donald Reis*** has recently identified a novel neurotransmitter, Agmatine, and he is studying the imidazoline receptor. ***Lonny Levin*** is interested in signal transduction by various forms of adenylate cyclase in *Drosophila* and vertebrate systems, as well as the role of cAMP in cross talk among receptor systems. He recently isolated a novel soluble adenylate cyclase.

**The Structure of the Nervous System and Neuroanatomy.** Understanding signaling among neural cells is greatly facilitated by understanding the connections among nerve cells at the anatomical level, an approach used by many members of the program. Notably, ***Virginia Pickel*** is interested in receptor mediated interactions mediated by opiates, catecholamines, and other neurotransmitters and their role in movement and reward. ***Teresa Milner*** is elucidating transmitter interactions in the septohippocampal pathway that underlie learning and memory.

**Signaling by Growth Factors.** Many aspects of the development and maintenance of the nervous system are controlled by cell-cell interactions, and many of these are mediated by peptide growth factors signaling. ***Barbara Hempstead*** is determining the role of adapter proteins that mediate interactions between neurotrophin receptors and intracellular responses in several tissues, including neurons and the cardiovascular system. ***John Wagner*** is interested in the role of the rho family of GTP-binding proteins in mediating the morphological responses to NGF and the transcription factors, including bHLH proteins regulated by NGF.

**Integrative Processes.** ***Keith Purpura*** is interested in how attention influences cortical processing and how neural assemblies can represent the external world and influence behavioral tasks. ***Fred Plum*** uses imaging and cognitive approaches to elucidate the cerebral processes involved in conscious processes. ***Jonathan Victor*** studies signal processing and information coding in the nervous system. ***Daniel Gardner*** combines neurophysiology and artificial intelligence to elucidate the principles used to form neural networks. He also develops computer databases and programs to promote information exchange among scientists and to facilitate integration of neuroscience data. ***Donald Reis*** has done seminal work in the integrative neural and neurochemical mechanisms controlling autonomic function, cerebral blood flow, and metabolism. ***Joy Hirsch*** uses fMRI, which measures changes in oxygen use in the brain, to map the response of the human brain to sensory stimuli.




*Newly generated neurons from adult human temporal lobe in phase contrast (A) and after immunostaining for the neuronal protein MAP-2 (B). After loading with the calcium indicator dye fluo-3 (C), depolarization increases fluorescence (D). (Goldman Laboratory)*

**Behavior.** Since the ultimate purpose of the nervous system is to regulate behavior, several members of the program are attempting to determine the structural and biochemical basis of behavior. ***James Gibbs, Gerard Smith,*** and ***Danielle Greenberg*** share an interest in the regulation of feeding behavior, including its regulation by neuroendocrine function, neuropeptides, and dietary fat.

**Metabolism and Neurotoxicology.** ***Arthur Cooper*** is interested in neurotoxicology, amino acid metabolism, and energy production in Alzheimer's Disease and during ischemia. ***John Blass*** studies inborn errors of metabolism, especially defects that contribute to the development of Alzheimer's disease. ***Rosario Trifiletti*** has a clinical interest in the metabolic basis of inherited diseases in children. ***Flint Beal*** is dissecting the neurotoxic activities of MPTP and 3-nitroproprionic acid. ***Gary Gibson*** has discovered fundamental differences that distinguish cells of Alzheimer's patients and is studying the potential role of thiamine in oxidative damage during neural degeneration. ***Peter Stokes*** studies the role of the pituitary-thyroid axis on affective disease and the role of lithium on bipolar disease.

**Vision.** The visual system is a premier system to study sensory processing in both the retina and the brain. Members of the Dyson Vision Institute, directed by ***Enrique Rodriguez-Boulan,*** have a special interest in this area. ***Chi-Hwa Sung*** is interested in the retinal dystrophies which cause blindness, especially how defects in protein targeting contribute to this pathology. ***Robert Duvoisin*** has isolated novel glutamate receptors that regulate retinal function by controlling 'on' and 'off' neuronal pathways. ***Enrique Rodriguez-Boulan*** focuses on the role of the retinal pigment epithelium in retinal function as well as the targeting of specific molecules in neural cells. ***John Wagner*** is determining the roles of growth factors in retinal development and injury. ***Jonathan Victor*** is interested in processing of visual information in both the retina and the cortex. ***Keith Purpura*** is interested in communication among the cortical areas involved in processing visual information, while ***Joy Hirsch*** uses functional MRI to understand how individual areas of the cortex are involved in the processing of visual information.

**Neural Disease.** The majority of the faculty in the program have strong interests in human neurological disease, and research in this area is fostered by the Institute for Human Neuroscience, directed by ***Fred Plum. Flint Beal*** studies mechanisms of neurodegenerative disease, including Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotropic lateral sclerosis, and stroke. ***John Blass*** is interested in the molecular basis of Alzheimer's disease and neural degeneration.

A large number of investigators are interested in stroke and cardiovascular disease. ***Bruce Volpe*** studies the effect of ischemia and trauma in pathological processes and changes in brain structure and function. ***Gary Gibson*** is interested in signal transduction and oxidative processes in neurodegeneration associated with Alzheimer's Disease, ischemia, and metabolic disease. ***Rosario Trifiletti, John Wagner,*** and ***Donald Reis*** have made significant progress in determining the role of nitric oxide in neural degeneration after ischemia. ***Rosario Trifiletti*** studies the glutamate cascade of excitotoxicity, and the

role of nitric oxide in multiple sclerosis, acute myotrophic lateral sclerosis, and seizures. ***John Wagner*** studies the protective roles of growth factors during nitric-oxide toxicity. ***Donald Reis*** has observed that stimulation of certain neurons can protect others from ischemia. ***Eugene Golanov*** studies the neural regulation of blood flow and energy utilization in the brain.

The neurobiology of cancer presents several problems that set it apart from other forms of this disease. ***Jerome Posner*** studies the antigenic responses to cancer that induce neural degeneration (para-neoplastic syndromes). ***Ronald Blasberg*** uses Positron Emission Tomography (PET) to image brain tumors and study their metabolism and develop therapies for brain tumors. ***Myrna Rosenfeld*** is interested in the molecular biology of primary brain tumors and uses both herpes and adenovirus vectors to replace mutated genes in these tumors. ***Michael Caudy*** studies the expression and function of transcription factors that control differentiation along the neural lineage in neuroblastoma. ***Henry Furneaux*** is interested in the HuR family regulation of gene expression occurring in tumor-associated neural degeneration.

***Miklos Toth*** uses genetic approaches to generate animal models of diseases such as anxiety disorders, obsessive compulsive behavior, aggressiveness in humans, and seizure. ***Jin Son*** is using neuron specific promoters to develop animal models of neurodegenerative disease and to produce neural tumors and cell lines in targeted neural populations.

Many faculty are interested in drug abuse and use of opiates for the control of pain. ***Michiko Okamoto*** is interested in the neuropharmacological basis of alcohol, benzodiazepine, and barbiturates. ***Ronald Blasberg*** uses PET to image opioid receptors, while ***Virginia Pickel*** and ***Teresa Milner*** study the localization of opiate peptides and their receptors at the ultrastructural level. ***Charles Inturrisi*** and ***Gavril Pasternak*** focus on the molecular basis of opiate receptor function, tolerance, and dependence.

## PROGRAM REQUIREMENTS

**Mission:** The Graduate Program in Neuroscience is a multi-departmental, multidisciplinary effort by faculty, students, and fellows to provide an outstanding education in neuroscience. We believe that graduate education is an important step on a career pathway that may be in academics, a specialized research institute, the pharmaceutical or biotechnology industries, government, business, or education. We expect our graduates to be able to think independently and creatively, to have a demonstrated ability to make important discoveries, and to communicate their ideas effectively.

**Admission:** Applicants to the program are expected to have had thorough undergraduate training in biology, organic chemistry, physics, and mathematics. Students entering this program after attaining an M.D. or a Masters' degree can have a modified educational program. Graduate Record Examination scores, transcripts, and supporting letters must be submitted with the application. Candidates considered for admission are invited to visit the program.

**Course of Study:** The program of research, course work, seminars, and independent study is individualized. Students are expected to spend time working closely with members of the faculty whose research approach is complementary to their interests. There are regularly scheduled seminars where work in progress is presented and discussed. By these means, the students are afforded the broadest possible view of the neurosciences during their graduate training.

Depending on their background and interests, students will be expected to take a course both in basic neuroscience and at least one upper level course in cell biology, molecular biology, biochemistry, or pharmacology. The Neuroscience Program offers courses in molecular, biochemical, cellular, and systems neurobiology. "Survey of Cell Structure and Function" is an interdisciplinary course that provides essential background for many entering students. Students will also select advanced graduate courses in the neurosciences and

related fields and undertake independent study to deepen their knowledge in areas of interest and develop a minor specialty. There is sufficient flexibility in choosing elective courses that students may specialize in a particular area(s), including molecular neurobiology, developmental neurobiology, systems neuroscience, neuropharmacology, or neurophysiology. Throughout their training, students are expected to participate in the weekly "Progress in Neuroscience" seminar series and the seminar companion course, "Current Topics in Neurobiology."

Each year, the program organizes an academic retreat which includes talks, poster sessions, and discussions. This retreat provides an informal setting away from the city where members of the program can interact and discuss their work. Senior students also present their work at the student organized du Vigneaud symposium and the Progress in Neuroscience Series.

**Laboratory rotations and thesis research:** Laboratory rotations allow students to experience research first-hand and to acquaint themselves with the research faculty of the Program. Students are expected to do two rotations of about two quarters each, but may do more rotations, before choosing their thesis advisor. Thesis research is guided by the students major sponsor and a committee that includes at least two additional faculty.

**Admission to Doctoral Candidacy:** Before the end of the second year, students will organize a Special Committee and take the qualifying (Admission to Candidacy) exam. In the Neuroscience Program, this exam is a defense of both the thesis research proposal and an original non-thesis research proposal.

# Pharmacology Program

## FACULTY

Joseph R. Bertino
Jochen Buck
Walter W. Y. Chan
Ting-Chao Chou
Tamara L. Doering
Diane Felsen
David W. Golde
Steven S. Gross
Lorraine J. Gudas
Hugh C. Hemmings, Jr.
Charles E. Inturrisi
Richard N. Kolesnick
Roberto Levi
Lonny R. Levin
Michiko Okamoto
Gavril W. Pasternak
Marcus M. Reidenberg
Arleen B. Rifkind
David A. Scheinberg
Kathleen W. Scotto
Francis M. Sirotnak
Hazel H. Szeto
Jon S. Thorson
Miklos Toth
C. Wilson Xu

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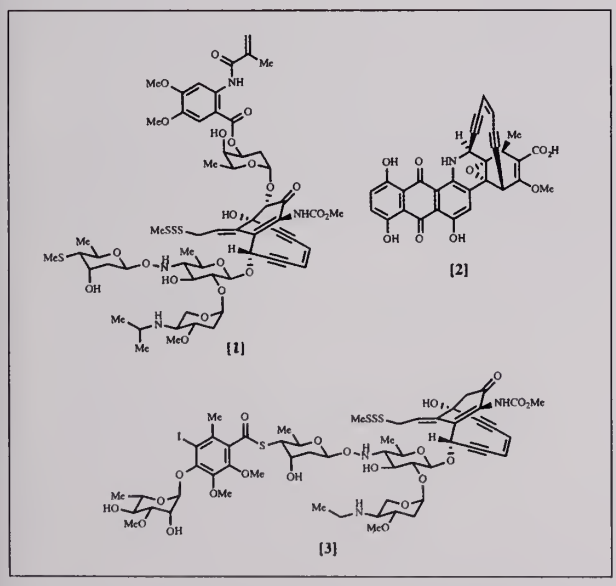
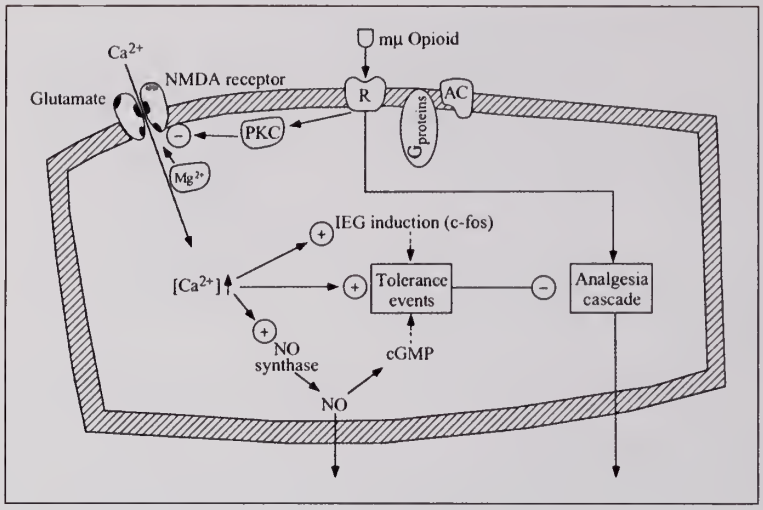
## OVERVIEW OF RESEARCH ACTIVITIES

The research activities of the Pharmacology Program are directed at understanding how drugs and chemicals modify biological systems. Drugs can act at many different levels of organization. At the level of gene expression, ***Dr. Gudas*** is learning how derivatives of vitamin A (retinoids) regulate both cellular differentiation and cellular proliferation during development and in the processes of tumor formation. ***Dr. Bertino*** is examining the role of oncogenes and tumor suppressor genes in the development of chemotherapeutic drug resistance. ***Dr. Scotto*** is studying the transcriptional regulation of the multidrug resistance (MDR) gene whose over expression is associated with clinical drug resistance. ***Dr. Xu*** has developed techniques to measure protein-protein interactions, and inhibitors of these interactions. ***Dr. Sirotnak*** focuses on the molecular mechanism of acquired resistance to antineoplastic agents, which has led to the discovery of a new and highly potent analog of methotrexate. ***Dr. Chou*** is investigating drugs that exert antitumor activity by virtue of their inhibition of tubulin. ***Dr. Toth*** has identified a gene involved in epilepsy and is studying how dysfunction of this gene leads to this disease. He is also creating transgenic mouse models to study other types of neurological diseases.




*Based upon labeling experiments, the confirmed precursors for the postulated polyketide-based enediynes esperamicin (1), dynemicin (2), and calicheamicin (3) include acetate, methionine and sulfate. (Thorson Laboratory)*

Often, the actions of drugs are mediated by specific receptors located on the cell surface or intracellularly. ***Dr. Pasternak*** is using molecular and biochemical techniques to characterize the receptors for analgesic drugs such as morphine. ***Dr. Inturrisi*** has found that NMDA receptor antagonists are able to prevent morphine tolerance and is examining how this receptor and the opioid receptors interact. ***Dr. Scheinberg*** is




*A model that presents some of the receptor-mediated signal transduction events that may be involved in the attenuation of morphine (mm) tolerance by NMDA receptor antagonists. (Inturrisi Laboratory)*

using monoclonal antibodies as drugs that specifically target sites on tumor cells, while ***Dr. Golde*** studies how cytokines regulate blood cell formation and the role of glucose transporters in neoplastic blood cells.

Receptors are linked to intracellular events by signal transduction pathways. ***Dr. Kolesnick*** has discovered a new signal transduction pathway, the sphingomyelin pathway, and is identifying how this pathway signals in response to receptor activation. ***Dr. Levin*** is investigating the biological role of individual isoforms of the second messenger, adenylyl cyclase, in learning and memory in Drosophila, while ***Dr. Gross*** is defining the actions of another intracellular messenger, nitric oxide, which mediates vascular homeostasis and regulates blood pressure. ***Dr. Rifkind*** is investigating how a cytoplasmic receptor for dioxin controls the expression of certain enzymes (cytochrome P-450s) and how this results in the diverse toxicity of dioxins and the polychlorinated biphenyls (PCBs). ***Dr. Buck*** has characterized two new intracellular messenger molecules, 14-hydroxy-retroretinol and anhydroretinol, and is studying their roles in the cell cycle and in malignant cells. ***Dr. Doering*** is interested in the role played by glycosyl phosphatidylinositol (GPI) in intracellular protein localization in central fungal pathogens that infect patients who are suffering from HIV.

At the systems level, ***Dr. Levi*** is examining the role of a novel histamine receptor subtype (the H3-receptor) found in human heart and activated in myocardial ischemia. ***Dr. Chan*** is searching for new drugs to prevent premature birth from among a group of selective oxytocin receptor antagonists. ***Dr. Szeto*** is developing novel opioid drugs for use as obstetrical analgesics. The drugs are evaluated for their effects on the mother and the fetus. ***Dr. Felsen*** is examining the mediators of inflammation in the genito-urinary tract, the receptors involved, and how new drug therapies can be designed for renal and bladder diseases. ***Dr. Hemmings*** is interested in the critical role played by protein phosphorylation in the effects of general anesthetics on synaptic transmission while ***Dr. Okamoto*** is involved in the development of new muscle relaxants for use during anesthesia. ***Dr. Thorson*** studies the biosynthetic pathways of natural products with antitumor activity in order to find ways to increase their production for research and therapeutic use. ***Dr. Reidenberg's*** clinical pharmacological studies are aimed at understanding the sources of variation in drug responses. He is also evaluating the mechanisms of the antineoplastic and antifertility effects of gossypol.

More complete information can be found under Faculty Research Descriptions.

## PROGRAM REQUIREMENTS

**Admission:** A baccalaureate degree with a strong background in the natural sciences and/or health sciences is required for admission. The Graduate Record Examination (verbal, quantitative, and analytical) is required for Ph.D. applicants, while the advanced test in Biology or Chemistry is strongly recommended.

**Course of Study:** In the first two years, students are required to complete the following core curriculum courses:

1. Cell Structure and Function
2. Introduction to Pharmacological Principles
3. Systems Pharmacology
4. Molecular Pharmacology of Cancer
5. Neuropharmacology
6. Biostatistics
7. Pharmacology Research Seminar.

Each student also completes at least one elective by June of the second year. This elective is selected from courses that are offered by other programs at the Graduate School.

**Program Supervision and Laboratory Rotations:** The Program Director and the Curriculum Committee will supervise the student's graduate program until the student selects a faculty member to serve as the major sponsor. Three laboratory rotations are required of each student. These rotations provide the opportunity for the student to participate in the diverse research activities that are available within the Program. This experience is designed to assist the student in the selection of major and minor sponsors for the thesis research.

**Admission to Doctoral Candidacy:** The Admission to Candidacy Examination consists of two parts: a written research proposal and an oral exam which includes discussion of the written proposal. It is expected that most students will take this exam by the end of May of their second year.

**Special Committee:** The Special Committee is comprised of a major faculty sponsor and two minor faculty sponsors. The Program Director will assist the student in the selection of the major (thesis) advisor.

**Retreat:** The Pharmacology Program holds a retreat each year in the spring, usually for two days at a country inn. Members of the Program gather for a series of informal talks and a poster session to exchange the latest scientific information. This provides a relaxed setting for new incoming graduate students to meet other graduate students, postdoctoral fellows, and faculty members in the department.

# Physiology, Biophysics & Molecular Medicine

## FACULTY

Olaf S. Andersen
Thomas J. J. Blanck
Daniel Catanzaro
Ronald G. Crystal
Daniel S. Duch
Daniel Gardner
Marvin C. Gershengorn
Bernice Grafstein
Doris A. Herzlinger
Xin-Yun Huang
Jason A. Koutcher
Gloria C. Li
C. Clifton Ling
Thomas Maack
Daniel R. Nussenzveig
Lawrence G. Palmer
Randi B. Silver
John L. Stephenson
Yi Wang
Alan M. Weinstein
Erich Windhager

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## OVERVIEW OF RESEARCH ACTIVITIES

Physiology is the science of biological function, of how living things work. Research in physiology, biophysics, and molecular medicine combines studies of function at the molecular and cellular levels with integration of this knowledge into analysis of organ systems and whole animals. A strong emphasis is placed on a quantitative understanding of each level of organization. These insights will eventually be applied to clinical medicine to aid in prevention, diagnosis, and treatment of human disease. The members of the Graduate Program in Physiology, Biophysics & Molecular Medicine study function at the molecular, cellular, and organ system levels using a wide variety of scientific disciplines that, in addition to physiology, include biochemistry, cell biology, computer modeling, molecular and cellular electrophysiology, molecular biology, neuroanatomy, neurophysiology, and nuclear magnetic resonance. The research interests of the faculty are concentrated in five areas of biomedical science: 1) the structure, function, and regulation of integral membrane proteins, including ion channels and hormone receptors; 2) intracellular electrolyte homeostasis, cell volume regulation, and renal function; 3) mechanisms of hormone action, receptor turnover, and gene regulation; 5) development and regeneration in the kidney and the nervous system; and 5) radiation biology.

***Dr. Andersen*** investigates the molecular mechanisms governing the function of membrane-spanning ion permeable channels. These questions are addressed using a combination of electrophysiological studies of channel function and spectroscopic studies of channel structure, in conjunction with theoretical/computational analysis of channel folding, ion permeation and channel-bilayer interactions.

***Dr. Blanck's*** research interests include the characterization of the effects of anesthetics on intracellular calcium distribution in cardiac and neuronal cells. These studies will further the understanding of how volatile anesthetics work to produce general anesthesia, their protective effects during ischemia, and their depressive effects on cardiac contractility.

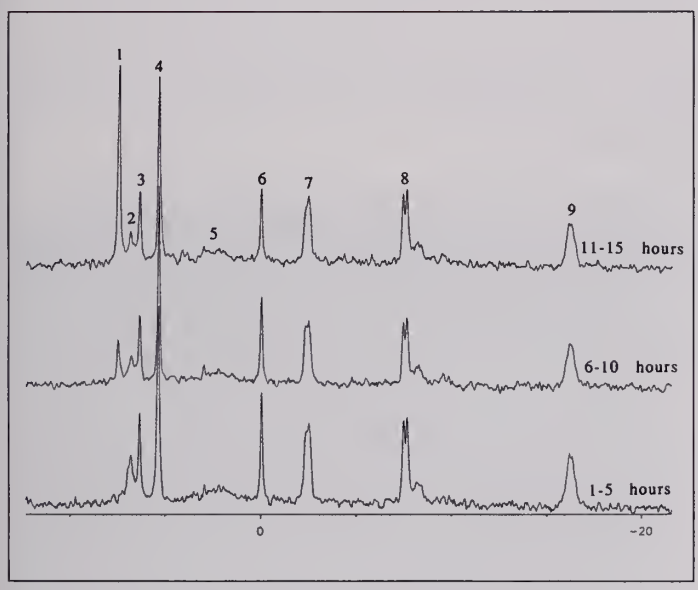
***Dr. Catanzaro*** investigates control of blood pressure by the renin angiotensin system. These studies focus on the molecular mechanisms that normally direct and regulate renin synthesis and secretion and disruptions that cause hypertension.

***Dr. Crystal's*** major research interest focuses on understanding, preventing, and treating hereditary and acquired human disorders by defining and modulating the genetic repertoire of somatic cells. To this end, his laboratory uses *ex vivo* and *in vivo* gene therapy strategies directed toward modulating gene expression relevant to pulmonary, cardiovascular, infectious, hematologic, and neoplastic disorders. The interests of the laboratory include design of gene transfer vectors, defining the interaction of gene transfer vectors with target cells, the mechanisms used by viruses to transfer their genome to the nucleus, and the development of chimeric promoters to control transgene expression.

***Dr. Duch's*** laboratory investigates the molecular interactions that define and control the functions of ion channels. This work reconstitutes purified and unpurified sodium channels from the electric organ of the electric eel and the human brain into planar lipid bilayers in order to probe the molecular interactions between the protein, and carbohydrate and lipid domains of these channels.

***Dr. Gardner's*** research has two goals: understanding how neuronal identity is related to biophysical properties and network connectivity, and how neuronal signals code information. A component of the NIMH's Human Brain Project, his lab is designing networked databases of neuronal descriptions and characteristic neurophysiological data, analogous to genome and sequence databases.

***Dr. Gershengorn's*** focus of research is to delineate the structure-function relationships of guanine nucleotide-binding protein-coupled receptors that are activated by peptides, thyrotropin-releasing hormone (TRH) and calcitonin, and of a virally encoded receptor that may be involved in the pathogenesis of Kaposi's sarcoma. Emphasis is placed on the use of receptors, mutants, and chimeras in these studies, and on molecular modeling of the hormone-receptor interactions.




*Nuclear magnetic resonance peaks arising from perfused cancer (RIF-1) cell treated with 6-aminonicotinamide, an analog of NAD. Peaks are assigned to ATP (7,8,9), phosphocreatine (6), inorganic phosphate (4), and phospholipid membrane precursors (2,3). Peak 1 arises from 6-phosphogluconate providing evidence that the pentose phosphate pathway is blocked by 6AN. (Koutcher Laboratory)*

***Dr. Grafstein's*** primary interest is in nervous system regeneration and development. Her current research seeks to define the role of the pia-arachnoid in regulating the extracellular environment of the brain, which may have a defining influence on neuronal growth and function. In particular, she is interested in calcium signaling between the pia-arachnoid and the neuronal-glial compartment of the cerebral cortex.

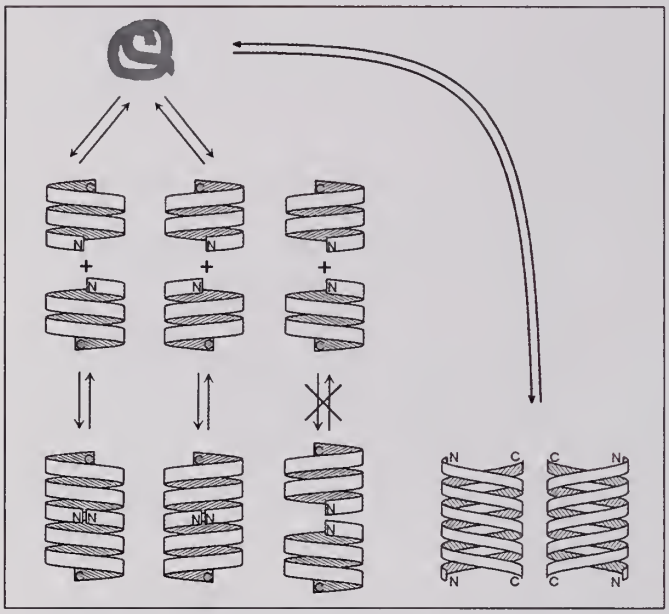
***Dr. Herzlinger's*** research program is focused on identifying the signals that enable embryonic cells to differentiate into the 14 different renal cell types required for normal kidney function. Utilizing the tools of molecular and cell biology, her laboratory has characterized embryonic renal stem cells, determined the stage at which these cells assume unique differentiated fates and identified a gene family that initiates their differentiation. Future directions in the lab include further characterization of the molecules required for kidney development and patterning during embryonic development.

***Dr. Huang's*** research focuses on signal transduction by heterotrimeric G proteins. The current focus is on direct stimulation of tyrosine kinases by G proteins, regulation of the Ras-family of small G proteins, genetic and biochemical dissection of the vertebrate G-protein-MAPK pathway, and regulation and function of ion channels.

***Dr. Koutcher's*** research focuses on *in vivo* applications of nuclear magnetic resonance (NMR) to the study of hematologic and neoplastic diseases. The focus of much of the work is to determine whether tumor metabolism, as monitored by *in vivo* NMR spectroscopy, can be used to 1) determine tumor sensitivity to anti-neoplastic therapy or 2) to enhance treatment by optimizing the choice or timing of therapy based on changes in tumor metabolism.

***Dr. Li's*** experiments have shown that of the many heat shock proteins (hsp's) preferentially synthesized after a heat shock, the concentration of hsp70 appears to correlate best with heat resistance, either permanent or transient. The long-term goal of this research is to establish the molecular basis related to the role that hsp70 plays in modulating cellular responses to heat and drugs or other environmental stresses.

***Dr. Ling*** is interested in the biological effects of radiation pertaining to application to radiotherapy. Current interests include the mechanism of radiation-induced apoptosis and the effects of c-myc and Ha-ras oncogenes on apoptosis.



*Folding pathways for the formation of membrane-spanning channels by sequence-substituted gramicidin analogues. A given peptide may form up to three different conducting channels, whose structures can be identified by single-channel electrophysiology. (Andersen Laboratory)*

***Dr. Maack's*** studies are directed to the elucidation of the physiology of atrial natriuretic factor (ANF), a hormone which plays an essential role in pressure-volume homeostasis, and its receptors. Recent work has focused on the structure-function relationships of two different types of receptors: CG receptors are involved in generation of the second messenger cGMP, while C-receptors participate in the removal of ANF from the circulation, and in this manner contribute importantly to the regulation of plasma levels of this hormone.

***Dr. Nussenzveig*** investigates the cellular traffic of G-protein coupled receptors (GPCRs) in polarized epithelial cells. He is currently delineating the mechanisms and molecular determinants that are responsible for the basolateral plasma membrane domain expression of the human calcitonin receptor (hCTR) in Madin-Darby Canine Kidney cells. He applies cell biological techniques to study expression of receptor mutants and strategies designed to detect protein-protein intermolecular interactions to identify factors involved in hCTR targeting.

***Dr. Palmer's*** research focuses on the mechanism of transepithelial $Na^+$ and $K^+$ transport by tight epithelia, and the control of this process by hormones. The major effort is to define the nature of the $Na^+$- and $K^+$-selective channels responsible for the movement of these ions across the luminal cell membrane of epithelia, and to identify the intracellular events that modify the function of the channels.

***Dr. Silver*** is interested in the role of intracellular $Ca^{2+}$ and $H^+$ in cellular homeostasis. The primary focus of the laboratory is in the application of fluorescence biotechnology to study intracellular pH regulation, as well as the variation in cytosolic $Ca^{2+}$ levels in renal cells as they relate to perturbations in acid-base state or electrolyte balance.

***Dr. Stephenson*** is interested in theoretical aspects of transport water and electrolytes in epithelia and in the kidney. Current studies focus on the relation of medullary concentration gradients and the osmolality of final urine in the mammalian kidney, and on the development of a mathematical model of electrolyte transport in the whole kidney, which includes electrolytes ($Na^+$, $K^+$, $Cl^-$, , $H_2PO_4^-$, $H^+$), glucose, urea, osmotic forces, hydrostatic pressure, and electrical potential.

***Dr.Wang's*** prime interests are the science and engineering of magnetic resonance (MR) imaging, and its applications in clinical practice. Currently he is developing techniques for imaging blood flow in large vessels (angiography) and in microvasculature (perfusion). These techniques are targeted for applications in cardiovascular diseases and neuro-functional mapping.

***Dr. Weinstein*** is interested in the theory of solute and water transport across epithelia, and the development of mathematical models that permit the computer simulation of normal and pathological conditions. The primary focus of this work is sodium reabsorption: the pathways and driving forces and the mechanisms by which cells maintain volume and solute composition despite fluctuations in solute transport.

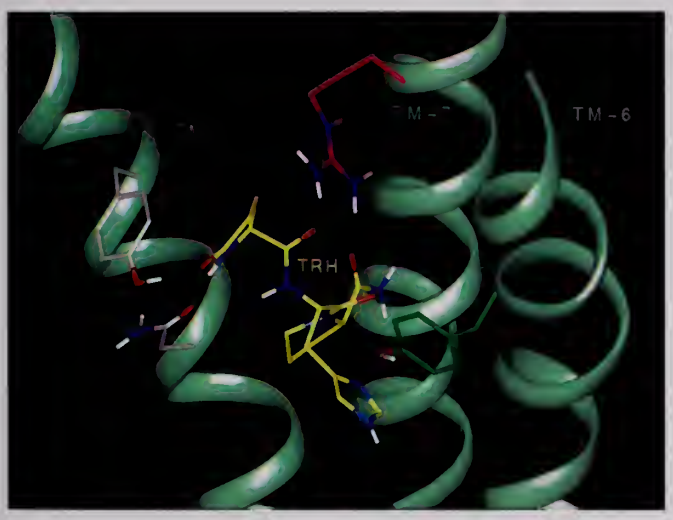
***Dr. Windhager's*** studies are aimed at elucidating the mechanisms of ion and water transport by renal epithelial cells, in particular the negative feedback regulation of sodium transport in cortical collecting tubules. Combining measurements of transepithelial sodium fluxes, intracellular ion concentrations by fluorescence methods and patch clamping of ion channels, it was concluded that cytosolic $Ca^{2+}$ and membrane voltage can account for the observed feedback control.

## PROGRAM REQUIREMENTS

**Admission:** Interested individuals are encouraged to contact the Program Director before preparing a formal application. Letters of inquiry should include a discussion of educational background and indicate possible areas of emphasis of graduate study. Applicants must have completed courses in biology, inorganic and organic chemistry, physics, and mathematics through the level of differential and integral calculus. Additional coursework in these disciplines at the undergraduate level is encouraged. The Graduate Record Examination is required and advanced subject tests are recommended. Applicants with otherwise exemplary records who lack certain course requirements will be considered for acceptance provided that they remedy their deficiencies while in training.

**Course of Study:** The Program emphasizes the importance of research and teaching in the preparation and development of individuals for careers in physiology, biophysics and molecular medicine. This goal is achieved by a combination of didactic courses, seminars, and supervised research leading toward the preparation of a thesis.

A special program of study will be developed for each student in consultation with his or her Special Committee. For M.D./Ph.D. students, the program takes into consideration their coursework during the first two medical school years. Students that enter with an M.D. or a Masters degree will likewise have specially adapted programs.




*Computer simulation of thyrotropin-releasing hormone (TRH) (yellow) in the binding pocket of the seven transmembrane (TM)-spanning TRH receptor. The four amino acid residues shown (Tyr106 in TM-3, Asn110 in TM-3, Tyr282 in TM-6 and Arg306 in TM-7) constitute the major contact sites for TRH. (Gershengorn Laboratory)*

In the first two years students are expected to complete satisfactorily a core curriculum. The curriculum will be determined by the student's previous coursework and likely research concentration. The curriculum usually will include:

1. Cell and Human Structure and Function
2. Molecular Basis of Disease
3. Selected advanced courses in membrane biophysics, cell physiology and systems biology
4. Elective courses in biochemistry, cell biology, molecular biology and neuroscience.

In addition, all students must complete three laboratory rotations, one of which is usually in the thesis advisor's laboratory.

A thesis advisor is usually chosen early in the second year. A Special Committee consisting of the thesis advisor and two other faculty members will be constituted to guide the student in his/her research preparation. Students start their thesis research before completing their formal coursework, but are not admitted to Ph.D. candidacy until passing the Admission to Candidacy Examination toward the end of the second year.

In later years, students will participate in small group teaching activities in graduate school and medical school courses.

For more program information see the WWW home page: http://physiology.med.cornell.edu.

# Master of Science Program in Clinical Epidemiology and Health Services Research

## FACULTY

Ronald D. Adelman
George S. Alexopoulos
John P. Allegrante
Josephine A.V.Allen
Mitchell J. Blutt
Gilbert J. Botvin
Robert M. Braude
Lawrence D. Brown
Martha L. Bruce
Mark A. Callahan
Mary E. Charlson
Oliver T. Fein
Joseph J. Fins
James P. Hollenberg
Donald S. Kenkel
John M. Kuder
Mark S. Lachs
Andrew C. Leon
Carol A. Mancuso
Charles E. McCulloch
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Stephen A. Paget
Margaret G. E. Peterson
Karl Pillemer
Laura Robbins
Eunice Rodriguez
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### Graduate Program Chairperson

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Program information: ssamuel@mail.med.cornell.edu.

## PROGRAM OVERVIEW

The program of study leading to the Master of Science (MS) degree in Clinical Epidemiology and Health Services Research is designed for those who wish to plan, implement, and analyze quantitative and qualitative research studies, using appropriate research designs. The core of the curriculum includes research methodology, biostatistical techniques, data management, decision analysis, health economics, and program evaluation. Graduates of the program will be prepared to pursue academic careers in a variety of settings where data are required to answer complex questions and assess outcomes. The emphasis is on training clinician researchers to teach research methods, conduct methodologically rigorous and scientifically sound studies, evaluate programs, and perform cost-effectiveness and cost-benefit studies in a variety of populations.

## PROGRAM REQUIREMENTS

**Admission:** Admission to the program in Clinical Epidemiology and Health Services Research requires an M.D. or a BSN degree, with three years of work experience and acceptance into the Weill Graduate School of Medical Sciences of Cornell University.

Application material must be completed and returned to the office of the Weill Graduate School of Medical Sciences together with (1) official transcripts of records from all colleges and universities attended, (2) a statement of purpose of graduate study, and (3) two letters of recommendation from individuals in academic positions who know the applicant professionally. In addition, scores from the Graduate Record Examination (GRE) or Graduate Medical Aptitude Test (GMAT) are required to aid in the evaluation of the applicant.

The completed application and all supporting documents will be screened initially by the Clinical Epidemiology and Health Services Research program faculty. Personal interview meetings will be scheduled and held with each potential applicant. Applications for July admission and all credentials, including official transcripts of records from all colleges and universities attended, must be received by the deadline of December 31. A nonrefundable fee of $50 is charged for filing an application for admission.

**Course of Study:** Eligibility for the Master of Science degree in Clinical Epidemiology and Health Services Research requires the satisfactory completion of no less than 30 credits of course work and the completion of an integrative project or a research thesis. After completion of the curriculum and culminating project, students will be required to defend their findings. The projects are at the core of the Clinical Epidemiology and Health Services Research program. The most important foundation for preparing individuals for future careers is the utilization of new skills and knowledge to conceive, design, and conduct research projects, with faculty guidance and support.

For full-time students, the two-year program begins with an intensive summer session, with the remainder of the course work completed during the subsequent fall and spring semesters. The second year is devoted to the development, administration, and analysis of the research or culminating project. The program can also be completed on a part-time basis—up to four years—to accommodate individuals with differing needs and limited time commitments. The format for each of the curriculum units is small-group seminars, with interactive lectures. Each of the sessions has required homework assignments; the candidate must successfully complete each assignment to pass the course.

**Tuition and Fees:** Tuition for the Masters Degree Program in Clinical Epidemiology and Health Services is projected to be $21,000 for the entire program. Tuition includes fees for matriculation and graduation expenses.

**Refunds:** Part of the tuition will be refunded if the student obtains official certification of leave of absence or withdrawal from the Graduate School of Medical Sciences during the semester. Students who terminate their registration during a regular term in this manner will be charged tuition from the registration day to the effective date of the certificate as follows: first week, 10 percent; second week, 20 percent; third week, 30 percent; fourth week, 40 percent; fifth week, 60 percent; sixth week 80 percent; seventh week, 100 percent. No charge will be made if the effective date of leave or withdrawal is within the first six days of the term.

**Fellowship Training Opportunity:** Health Services Research Training Fellowships are available for physicians who have completed an accredited residency training program in any clinical area. The program is open to citizens and permanent residents of the United States. The program seeks physicians who are committed to the application of health services research and clinical epidemiology to the improvement of health care and who are committed to pursuing a research career. This fellowship is administered through the Division of General Internal Medicine, at the Weill Medical College of Cornell University.

# Course Offerings

# Biochemistry & Structural Biology

**Biochemistry & Structural Biology.** A formal advanced biochemistry course offered jointly by Molecular Biology, Cell Biology & Genetics, and the Biochemistry & Structural Biology Programs. Biochemistry and Structural Biology is a two-quarter course which is part of the core requirements of the Program. The course covers equilibria, bond formation, protein chemistry and structure, nucleic acid chemistry and structure, ligand binding, chemical and enzyme kinetics, enzyme reaction mechanism, principles of macromolecular analysis, principles of protein purification, and principles of macromolecular recognition and specificity. Drs. Marians, McGraw, Pavletich, Shuman, and staff.

**Structural Analysis.** This course will cover the structure, folding and interactions of proteins with the emphasis on relating structure to biological function. Biophysical techniques will be introduced and their applications outlined. Dr. Pavletich and staff.

**Protein-Nucleic Acid Interactions.** This course will cover known structures of protein-DNA and protein-RNA complexes and their role in replication, transcription, translation, and recombination of the genetic code. Dr. Patel and staff.

**RNA World.** This course consists of lectures, discussions, and assigned reading. RNA evolution from a primitive, all-RNA system to the present one and RNA:RNA interactions, both structural and enzymatic, are considered, leading to detailed discussions of RNA enzymes (ribozymes) and their substrates. The course emphasizes RNA:protein interactions and the functional motifs involved. RNA domains considered include ribosome binding sites; double-stranded RNA interaction regions; targets for other specific RNA-binding proteins; and the interactions involved in RNA splicing. Dr. Robertson.

**Membrane Biology.** This course covers the fundamental concepts involved in the chemistry and physical properties of lipids and carbohydrates. Metabolic aspects of carbohydrates and lipids will be discussed. Structure-function relationships during membrane biogenesis will be covered including the molecular aspects of membrane fluidity, membrane dynamics, and protein-lipid and protein-protein interactions. Drs. Maxfield, McGraw, and Ryan.

**Introduction to Research.** Laboratory rotations in experimental biochemistry dealing with the isolation, synthesis, and analysis of substances of biochemical importance (enzymes, proteins, nucleic acids, lipids, and metabolic intermediates), and study of their properties by various chemical and physical techniques. The student obtains this varied research experience by spending approximately two months in the laboratory of each of three faculty members of his or her choice. For incoming graduate students majoring in Biochemistry & Structural Biology.

**Biochemistry & Structural Biology Journal Club.** This meets weekly during the academic year and is required for all graduate students. Students and postdoctoral fellows meet with faculty supervision to discuss recent papers of biochemical importance. Student participation involves the presentation of papers and critical discussion of their contents and significance. Drs. McGraw and Rosen.

**Biochemistry Seminars.** A seminar series in which students, faculty, and invited scientists from this and other institutions report on progress in their laboratories.

**Biochemistry and Structural Biology.** A formal advanced biochemistry course is offered jointly by the Molecular Biology and the Biochemistry and Structural Biology Programs. Biochemistry and Structural Biology is a two-quarter course which is part of the core requirements of the program. The course covers equilibria, bond formation, protein chemistry and structure, nucleic acid chemistry and structure, ligand binding, chemical and enzyme kinetics, enzyme reaction mechanism, principles of macromolecular analysis, principles of protein purification, and principles of macromolecular recognition and specificity. Drs. Marians, McGraw, Pavletich, Shuman, and staff.

# Cell Biology & Genetics and Molecular Biology

**Molecular Genetics.** The course is organized around the principles of genetic analysis, with examples chosen from organisms that best illustrate those principles. The course is based on lectures and problem sections. The topics to be covered include: the nature of the gene; linkage and physical maps; chromosome structure and segregation; recombination mechanisms; nature of mutations; mutations as tools to dissect gene function; transposition; genetic analysis of the regulation of gene expression. Dr. Anderson and staff.

**Cell Biology.** This course explores key aspects of cell biology at a detailed molecular level. The focus is on the integration of structure/function relationships for proteins in cell membranes, cytosol, and nucleus. Specific topics include: membrane structure; protein biosynthesis and vesicular trafficking; cell architecture and motility; receptor and oncogene mediated signaling; intercellular interactions; cell-cell adhesion; and the cell cycle. The course consists of two lectures per week plus one interactive discussion section involving current research papers. Drs. Resh, Massagué, Brennwald, and staff.

**Gene Structure and Function.** A two-quarter course that explores the regulatory mechanisms governing the flow of information in cells from DNA to RNA to protein. The first module of the course deals with DNA replication, recombination and repair, and introduce basic principles of DNA topology and protein-DNA interactions as they apply to these and other processes. In the next module, the fundamentals of gene structure and transcription are presented. Topics to be discussed include: structure and function of transcription factors and RNA polymerases; mechanisms of transcriptional activation and repression; transcriptional control of the cell cycle; and the effects of chromatin structure on transcription. The final module covers post-transcriptional processing of RNA, including its translation into protein. Topics include: RNA splicing and editing, polyadenylation; mRNA transport and finally, regulation of translation. Drs. Fisher, Freedman, and staff.

**Logic and Critical Analysis.** This course is designed to teach the critical analysis necessary to be a successful scientist. Student reads papers in the primary literature and discuss the experiments. Questions addressed are: what was the hypothesis, what were the experiments designed to test, what other information is necessary to interpret the experiment, do the experiments accomplish this goal, what problems exist in the experiment, and where might you go from here? To develop the critical analysis skills required, the first group of presentations will emphasize one or two figures in each paper. Following development of critical skills required to read the primary literature, two to three papers will be assigned as a thematic group by each instructor to be discussed sequentially. Dr. Koff and staff.

**Graduate Research Seminar.** This course represents an opportunity for the faculty and students of the Molecular Biology and Cell Biology & Genetics Programs to hear the upper-class students describe their research in formal seminar presentations. Dr. Benezra.

**Nucleic Acids Enzymology.** A formal course presenting the enzymological mechanisms and control of prokaryotic and eukaryotic transcription and DNA replication. Enzymes which alter DNA structure and shape are reviewed and topics in DNA repair and recombination are also covered. Drs. Marians, Hurwitz, and staff.

**Molecular Virology.** A formal course in which major emphasis is placed on the basic mechanisms in the biology of all animal viruses, including RNA and DNA tumor viruses. The topics considered include: virus structure and composition; assay of viruses and viral-specific products; transcription and replication of viral nucleic acids; translation of virus-specific proteins; assembly of viral particles; structural and functional alterations in viral-infected cells, including transformation, pathogenesis of viral diseases, and viral genetics. Drs. Falck-Pedersen, Shuman, and staff.

**Molecular Biology of Cancer.** This course presents an in-depth analysis of the mechanistic basis of cancer: the nature of the neoplastic cell phenotype, the genetic alterations found in cancer cells, and the functional mechanisms by which these alterations contribute to tumorigenesis. After an introduction to hereditary, viral, and environmental risk factors in cancer, the key role of deregulated cell-cycle checkpoints is discussed, together with the mechanisms by which oncogenes and tumor-oppressor genes affect growth regulation, apoptosis, and DNA repair . Examples of specific types of malignancy are used to illustrate human cancer genetics, tumor progression, and the role of DNA rearrangements and genomic instability. Other topics include mechanisms of invasion, metastasis, and tumor angiogenesis. The final module of the course considers how our understanding of the molecular basis of cancer can lead to novel methods of cancer therapy and prevention. The course format is a combination of lectures and discussion groups. Dr. Brown and staff.

**Developmental Biology.** Key concepts in developmental biology are presented and discussed in a number of model developmental systems including Drosophila, Xenopus, C. elegans, chick, and mouse. The course concentrates on early embryogenesis, patterning, and organogenesis and stresses genetic, cellular, molecular, and comparative approaches to problems in development. Specific topics include axis determination, gastrulation, neurulation, and development of model organ systems such as muscle, limb, eye, heart. The course consists of weekly lectures and weekly interactive group discussions of classic and current research papers. Dr. Niswander and staff.

**Special Topics in Advanced Genetics.** Specialized topics in advanced genetic analysis will be covered. Each four week module will include both lectures and discussion of recent papers from the literature on a focused topic. Topics will change from year to year. Examples of topics to be covered include: gene silencing in yeast and Drosophila; imprinting and X inactivation; sex determination; DNA repair and cancer genetics; genetic analysis of Drosophila wing development; and genetic analysis of mammalian development. Dr. Anderson and staff.

# Immunology

**Fundamental Immunology.** Quarters I and II of the course provide a comprehensive overview of basic immunology beginning with the specific interactions of target cells and T cells that are regulated by the MHC molecule and peptide antigens on the target cell and the antigen-specific T-cell receptor. The development of antigen-specific T cells in the thymus and their activation in the periphery, plus the development and activation of B cells are covered in detail. Specific roles for cytokines or lymphokines in the immune response are also important topics. Quarters III and IV of the course cover the contribution of innate and antigen non-specific mechanisms of host defense and topics of clinical relevance, such as microbial immunity, allergy, autoimmunity, tumor immunology, congenital and acquired immunodeficiencies, transplantation immunology, and aging. Dr. Casali and the Immunology Faculty.

**Advanced Topics in Immunology.** This course, in modular format, is designed to teach selected topics, in depth, including historical overviews, underlying principles, current status, and significance for contemporary Immunology. Moreover, attempts will be made to connect immunological specialization with general principles of Biology and Biochemistry. The course will be open to all students and postdoctoral fellows. First and second year students will be required to take two modules for credit. Planned topics will include signal transduction, apoptosis, tumor immunology, and developmental immunology. Other modules will be added *ad hoc*. The Faculty of the Immunology Program.

**Immunology Graduate Research In Progress Seminar.** This course is designed to provide all Immunology Program graduate students with experience in preparing and giving oral presentations. Each student is required to give several talks based on various topics from their research and the current literature. Dr. Chen-Kiang.

# Neuroscience

**Genes, Drugs, and the Brain (GD&B).** This is a year-long, integrated series of independent courses that will provide interested students with a working knowledge of fundamental neuroscience. Each course is self-contained, and each may be taken individually. Each course is described below. The series includes: Molecular and Cellular Neuroscience (Quarter 1 and 2); Structure of the Nervous System/Biogenic Amines, Addiction, and Integrated Behavior/Excitation and Inhibition in the CNS (Quarter 3); Neuropeptides (Quarter 4a); and Cholinergic System, Motor Control, Learning, and Behavior (Quarter 4b).

**Molecular and Cellular Neuroscience (GD&B 1).** The course will emphasize the molecular, cellular, and biochemical research opportunities in the nervous system. Topics covered include: regulation of gene expression in neurons and glial cells, control of neurotransmitter synthesis, the biology of the synapse, signal transduction by cell surface receptors, polarization of neurons, axonal transport, membrane potential, and neurophysiology. It is generally taken in the first year by neuroscience students, but it is also appropriate for second year students from other programs who want an introduction to neuroscience. Dr. Sung.

**Structure of the Nervous System/Biogenic Amines, Addiction and Integrated Cell Behavior/Excitation, and Inhibition in the CNS (GD&B 2).** This course combines consideration of the structure of the nervous system and the neuropharmacology of neurotransmitters in the context of the function of the nervous system. It provides an introduction to neuroanatomy and a more detailed consideration of receptors for the biogenic amines, GABA, and glutamate. Drs. Toth, Baker, and Grafstein.

**Neuropeptides (GD&B 3a).** This mini-course considers the unique features of neuropeptides as neurotransmitters and neuromodulators in the CNS as well as their role in neuroendocrine regulation. It will focus on opiates and pituitary peptides as specific examples of this large class of signaling molecules. Drs. Inturrisi and Szeto.

**Learning, Memory, Motor Control, and Behavior (GD&B 3b).** This course will describe cholinergic and NOergic neurons and attempt to show how the nervous system integrates sensory input and produces behavior. Completion of some of the earlier parts of this series or extensive independent study will be necessary to appreciate this material. Dr. Gibson.

**Cell Structure and Function.** The objective of this interdisciplinary course is to present our first year graduate students with basic principles of cell function as described by biochemistry, cell and molecular biology, molecular pharmacology, and electrophysiology. It is intended to lay a foundation for more specialized courses and laboratory research. The course consists of lectures, journal clubs, experimental design sessions, and small group discussions. It is taught by faculty from throughout the graduate school of medical sciences. Drs. Pardee and Wagner.

**Research Proposals and Scientific Journalism: Inspiration, Writing, and Evaluation.** This seminar course will provide students with experience in developing and writing both a popular science article and a research plan in an area of their own choosing. Students will also critically evaluate the merits of specific approaches to scientific problems. It will meet about eight times during the third and fourth quarters, but requires submission revised assignments between classes. Drs. Wagner and Weil.

**Research Rotations in Neuroscience.** Neuroscience students who have arranged for a research rotation must register for this course each quarter the rotation is conducted. The student must submit a one page description of the proposed research in the first two weeks of the rotation and submit a 3-5 page description of the research that has been completed as soon as the rotation is finished. The faculty member will provide a 1-2 page commentary on the accomplishments of the student during the rotation. Students meet at the beginning of each quarter to describe their current rotation project. Faculty of the Graduate School.

**Developmental Neurobiology.** This course explores fundamental concepts in the development and maintenance of the nervous system. Major topics include classical neuroembryology, inductive effects, cell lineage, determination of cell fate, axonal guidance, synaptogen-

esis and specificity of synapse formation, cell-cell interaction, and naturally occurring cell death. It is coordinated with the course in Developmental Biology offered by the Program in Cell Biology and Genetics. Dr. Goldman and faculty of the Program in Neuroscience.

**Pathobiology of Neurological Disease.** This course will review the basic pathophysiology of important neurological diseases. The course will focus on complex disease processes that are best approached from a multidisciplinary point of view. Topics may include stroke, multiple sclerosis, epilepsy, Alzheimer's disease, Parkinson's disease, and selected behavioral or psychiatric disorders. The course will consist of both lectures and informal discussions of recent research papers. It is designed to be taken in sequence with Molecular Basis of Neurological Disease and is open to medical students as an elective. Dr. Plum and faculty of the Neuroscience Program.

**Molecular Basis of Neurological Disease.** This course will review current attempts to understand neurological disease from a molecular point of view. Students will learn how to apply the basic methods in molecular biology and molecular genetics to the study of neurological disease. Topics will include muscular dystrophy, myotonic dystrophy, myasthenia gravis, Alzheimer's disease, Huntington's disease and Charcot-Marie-Tooth disease. The course will consist of lectures, critical discussions of recent research papers and the preparation of an original research paper. This course is designed to be taken in sequence with Pathobiology of Neurological Disease. Drs. Furneaux and Goldman.

**The Visual System.** The visual system offers marvelous opportunities to study fundamental problems in neuroscience. These seminar courses, which vary from year to year, offer lectures and readings on current research topics in the vertebrate visual system. In 1998-1999 this course will focus on "Advanced Topics in Vision Research" (QIII, IV). In 1999-2000, the course will consider "Systems Neurophysiology" (QII-III at Rockefeller University) and "Visual Processing" (QIV). Dr. Jonathan Victor organizes every year a "Mini-rotation in Ophthalmology" with clinical faculty from the Department of Ophthalmology. Drs. Rodriguez-Boulan and Victor, with faculty of the Tri-Institutional Training Program in Vision Research.

**Mathematical Methods in Neuroscience.** This course provides a didactic introduction to a variety of mathematical approaches in neuroscience, selected both because of their proven usefulness and their intrinsic interest. Mathematical structures traditionally considered "advanced" will be introduced in an elementary fashion. Applications to be considered will include the analysis of channel activity, the analysis of spike trains, and image analysis. Dr. Victor.

**Functional Neuroimaging.** Current developments in imaging technology (magnetic resonance imaging, MRI, and positron-emission tomography, PET) open a new window of opportunity for neuroscientists to observe localized neural activity and to study neural organization in the human brain. The aim of this course is to introduce the fundamental principles of functional imaging (with a particular emphasis on MRI and PET) and to survey the literature and emerging new developments in neurobiology. Students will have an opportunity to observe and participate in on-going functional MRI investigations. Dr. Hirsch and faculty of the Neuroscience Program.

**Proseminar in Synaptic Physiology.** See Course Offerings for Program in Physiology and Biophysics for description.

**Progress in Neuroscience.** This course is the seminar series in the Program in Neuroscience. Most lectures are given by speakers invited from outside the Cornell community, but speakers are also drawn from the Program in Neuroscience and scientists at Cornell with related interests. Dr. Duvoisin and the seminar committee.

**Progress in Neuroscience/Current Topics in Neurobiology.** This course combines the seminar series in the Program in Neuroscience with critical discussions of papers published by the speaker, or related papers in the area of that week's seminar. Faculty of the Neuroscience Program.

# Pharmacology

**Cell Structure and Function.** The objective of this interdisciplinary course is to present our first year graduate students with basic principles of cell function as described by biochemistry, cell and molecular biology, molecular pharmacology, and electrophysiology. It is intended to lay a foundation for more specialized courses and laboratory research. The course consists of lectures, journal clubs, experimental design sessions, and small group discussions. It is taught by faculty from throughout the graduate school of medical sciences and is required for all incoming Pharmacology students. Drs. Pardee and Wagner.

**Biostatistics.** The course is targeted at individuals involved in clinical and biomedical research. The course consists of lectures and discussions on exploratory data analysis, basic concepts of statistical analysis, construction of hypothesis tests and confidence intervals, the development of statistical methods of analyzing data, and development of mathematical models used to relate a response variable to explanatory or descriptive variables. Dr. Heller.

**Introduction to Pharmacological Principles.** This course is designed to familiarize the student with concepts somewhat unique to pharmacology. This introductory graduate student course emphasizes general concepts in receptor theory, dose response relationship, mechanisms of drug action and resistance, pharmacokinetics, metabolism, tolerance, and dependence. All first year graduate student in Pharmacology are required to take this course. This course is integrated with the Cell Structure and Function Course in terms of subject matter. Drs. Gross and Thorson.

**Systems Pharmacology.** This course focuses on the physiology and pharmacology of the cardiovascular, respiratory, urinary, gastro-intestinal, and endocrine systems. Dr. Chan.

**Molecular Pharmacology of Cancer.** This course examines drug action at the molecular level, particularly with respect to cancer therapeutics, and consists of both lectures and reviews of current journal articles. Topics include mechanisms of drug resistance, oncogenes and tumor suppressor genes, computer based drug design, immunotherapy, hormone therapy, differentiation agents, tumor promotion and environmental toxins, tumor angiogenesis, and tumor metastasis. Drs. Bertino and Scotto.

**Neuropharmacology.** This course consists of modules 3 and 4 of the Genes, Drugs and the Brain (GD&B) course. This course is jointly sponsored by the Neuroscience and Pharmacology Programs. It is designed to present current concepts of the major central nervous system (CNS) neurotransmitters and their functional neuroanatomy. The course will integrate discussions of the mechanisms of neurotransmitter biosynthesis and release, receptor signal transduction and the alterations produced by CNS drugs. Dr. Toth and Neuroscience faculty.

**Pharmacology Research Seminar.** Topics of contemporary pharmacological interest and new concepts and methodological approaches in biological research will be presented by guest speakers from universities, pharmaceutical companies, and pharmacology faculty members. The presentations are followed by a discussion session which provides an opportunity for students to meet and talk to leading scientists in the field. Details of events will be announced in advance. Dr. Buck.

**Research in Pharmacology.** Research opportunities may be arranged throughout the year for graduate students who are not majoring in pharmacology but who want some investigative experience in the discipline. Special opportunities are offered for work on the nervous and cardiovascular systems and in biochemical and clinical aspects of pharmacology.

**Pharmacology Journal Club.** This is an informal course, designed to improve skills in critical reading and oral presentation of scientific information. It is organized and administered by the graduate students in the Pharmacology program and continues throughout the academic year.

# Physiology, Biophysics & Molecular Medicine

**Cell and Human Structure & Function.** Lectures, conferences, and journal clubs on molecular and cellular physiology, pharmacology, endocrinology, biochemistry, cell and molecular biology of cells and tissues of the cardiovascular, respiratory, urinary, and gastrointestinal systems. Drs. Maack, Palmer, and Pardee.

**Molecular Basis of Disease.** This course presents a detailed analysis of a small number of diseases from the molecular level through to the clinical illness including new approaches to therapy. Patients will be presented/interviewed. Normal physiology and pathological biology of the affected cells/tissues/organ systems will be reviewed. Emphasis will be placed on understanding the molecular details of the pathogenesis of each disease. Drs. Gershengorn and Nussenzveig.

**Molecular and Cellular Electrophysiology.** This course examines the electrophysiological properties of channels, cells, and simple systems. The aim of the course is to integrate the electrophysiology of single molecules with that of isolated cells and assemblies of cells, with emphasis on nerve, muscle, and epithelia. Topics to be covered include: the genesis of resting membrane potentials and action potentials; synaptic transmission and neuronal integration; epithelial ion transport; sensory transduction; and modulation of electrical activity. Drs. Andersen, Gardner, and Palmer.

**Advanced Topics in Membrane Biophysics and Ionic Channels.** A seminar series that addresses biophysical problems from a quantitative point of view. The aim is to train students in biophysical concepts, in particular the mathematical and experimental approaches relating to ion channel function. Dr. Andersen.

**Mathematical Models of Membrane Transport.** The general, thermodynamic description of membrane and epithelial transport will be reviewed. Comparison with kinetic descriptions of membrane transport will be considered, and the analysis of composite membrane systems will be examined as a prelude to the construction of epithelial simulations. Examples of such simulations will be used to examine transport along the kidney tubule under normal and pathological conditions. Dr. Weinstein.

**Proseminar in Synaptic Physiology.** The biophysics of synapses and their relation to behavior are explored by reading and discussion of seminal papers in the original literature. The first half of the course examines a model synapse, the mammalian neuromuscular junction, by intracellular recording, voltage clamping, noise analysis, and patch clamping. Topics in the second half include NMDA receptors, plasticity, and neural networks. Dr. Gardner.

# Clinical Epidemiology and Health Services Research

REQUIRED COURSES

**Introduction to Research Methodology and Statistical Analysis.** The basic architecture of clinical and health services research will be presented. Emphasis will be placed on the three critical components: the population; the interventions; and the outcomes. Basic principles of measurement for categorical and continuous data, including the sources of variance and hypothesis-testing for such data, will be emphasized. Participants will also learn about Type I and Type II error. Faculty: Mary E. Charlson, M.D., Margaret Peterson, Ph.D., Ted Szatrowski, M.D. 3 credits.

**Practical Applications and Computer Lab.** An approach to computer technologies to facilitate the design, implementation, and data analysis of research projects will be covered. Methods of data collection, including data coding and error checking will also be addressed. The course is taught in a computer laboratory and is designed to outline a rational approach, with emphasis on both the pitfalls and potential of utilizing the computer. The course will also involve primary data collection in the areas of chart review, medical claims data, health survey questionnaire data, and clinical trial data. Faculty: Pamela Williams-Russo, M.D., MPH, Margaret Peterson, Ph.D., Carol Mancuso, M.D. 2 credits.

**Introduction to Health Services Research.** This course introduces students to critical issues in health organization, financing, and policy which constitute the core of health services research topics. Students are prompted to consider the importance of the interrelationships between these issues and to apply critical thinking to the research. A variety of research methods and perspectives are presented to give students a flavor of the richness of this field. Specific topics include research areas of access and equity issues, evaluating health care quality and medical outcomes, health insurance and managed care effects on patient and physician behavior, and the evaluation of health care technologies and innovations. The course emphasizes the applied usefulness of research for policy making and organizational planning. Faculty: John Kuder, Ph.D. 2 credits.

**Clinical Economics.** The techniques used by health economists and other health services researchers to evaluate the economic attributes of a program or intervention will be examined. Students will learn how to critique cost-identification, cost of illness, cost-benefit and cost-effectiveness studies, and use these techniques in their own research projects. Faculty: Hirsch Ruchlin, Ph.D. 1 credit.

**Behavioral Science and Health Education.** This course will examine the applications of behavioral science and health education in a wide range of clinical medical problems and health promotion and disease prevention programs. Several theoretical models from the behavioral and social sciences will be reviewed. The course will also familiarize students with the concepts and basic steps used to develop and evaluate theory-based health education interventions. Faculty: John P. Allegrante, Ph.D. 2 credits.

**Qualitative Research Methods.** Students will gain a basic fluency with qualitative research methods, a research tool for gathering and interpreting descriptive data from surveys, focus groups, and face-to-face interviews. The sessions will interweave the theoretical underpinnings of the methods with examples of qualitative research applications. The nexus between qualitative research and techniques of anthropological, sociological, and historical research will be explored. The use of qualitative methods in action or practice situations, and their application as a prelude to quantitative methods, is stressed. Faculty: Laura Robbins, DSW. 1-3 credits.

**Decision Analysis.** The basics of probabilistic thinking and the concept of heuristics will be reviewed. Students will learn the five-step process, specifically, the structuring of the problem, the application of probabilities, the application of values, the calculation of expected utilities, and the sensitivity analysis. Faculty: James Hollenberg, M.D. 2 credits.

**Advanced Biostatistics.** The objective of this course is to convey basic concepts underlying multivariate analysis, with an emphasis on the handling of dimensional data. Considerations in dealing with survival analysis, odds ratios, and risk ratios are also covered in the course. Faculty: Ted Szatrowski, M.D. 3 credits.

**Advanced Seminar in Health Services Research.** Attended by students and their primary faculty supervisors, students learn how to formulate and design their own research project, while critiquing and helping their colleagues. This provides the opportunity for students to learn from each other's experiences. Students will use the structured opportunity of the colloquium to discuss their work and support each other in the development of their theses. Faculty: Mary Charlson, M.D. and Pamela Williams-Russo, M.D., MPH. 1-6 credits.

**Ethics of Clinical and Health Services Research.** The objective of this course is to convey the critical issues in the ethical conduct of research. It will focus on key issues in clinical and health services research including conflict of interest, preserving confidentiality, and assuring data integrity. The course will review historical events which led to the enactment of legislation and the development of health policies governing the conduct of research. Office of Misconduct Case-studies will be reviewed, including the renowned Tuskegee Syphilis study. Students will learn how to handle research data. Participants will also learn how to develop study protocols which comply with Institutional Review Board standards. Faculty: Joseph Fins, M.D. 1 credit.

**Teaching How to Teach.** Students will participate in a series of multi-component seminars using mini-lecture, videotape review, and role play formats to acquire new skills. The topical content includes effective ways to handle the Learning Climate, Control of the Session, Communication of Goals, Promoting Understanding and Retention, Evaluation, Feedback, and Self-Directed Learning. The course imparts practical skills immediately useful to clinical teachers. Faculty: Carol Storey-Johnson, M.D. 2 credits.

**Multicultural Approaches to Community Health and Disease Prevention.** This course is designed to provide an overview of cultural diversity, sensitize participants to their own cultural preferences, and explore how culture mediates health behaviors. The impact of culture on the development and implementation of health promotion policies, programs, and health services research will be explored. Faculty: Laura Robbins, DSW. 2 credits.

ELECTIVE COURSES

**Health Economics.** The objective of this course is to teach students to understand basic economic concepts and their relevance to the health care sector, and to learn to evaluate critically economic analyses reported in the health services research literature. It will also provide basic information in terms of how to design and carry out a health services research project incorporating an economic analysis. Faculty: Hirsch Ruchlin, Ph.D. 1 credit.

**Practical Issues in Health Services Research.** Hands-on discussion of strategies to deal with the nitty-gritty problems that occur in the conduct of research, including strategies for locating and recruiting study patients, finding and following up on data, handling missing data and other such issues that arise in clinical and health service research settings. Faculty: TBN. 1 credit.

**Critical Review of Current Clinical Epidemiology and Health Services Research.** The objective of this course is to review, evaluate, and synthesize new information appearing in the clinical epidemiology and health services research literature. Faculty: TBN. 1 credit.

**Health Policy and the Political System.** Students will learn how to analyze the role of major institutions, such as the central government, the federal system, the private sector, and special interests groups, in formulating and implementing health policy in the United States. Discussions of underlying normative issues and cross-national perspectives will also be covered. Faculty: Lawrence Brown, Ph.D. 2 credits

**Advanced Survey Design.** This course reviews survey research methods for collecting, analyzing, and evaluating health survey data. Topics include sampling theory, questionnaire design, interviewing techniques, and methods of survey administration. Faculty: John P. Allegrante, Ph.D. and Martha Bruce, Ph.D. 2 credits.

**New Business Development in Health Care.** Students will learn how to conduct competitive analyses, estimate market share, develop management structures, and formulate financial forecasts and capital needs. This applied course offers Students the opportunity to get hands-on training and expert guidance while developing their own business plans. Faculty: Mitchell Blutt, M.D., MBA. 3 credits.

**Principles and Practices of Communicating Research Results.** The objective of this course is to teach techniques for oral and written presentation of data. Students learn how to organize the results in order to convey optimally the significance of the findings. Topics include abstract writing, graphic presentation of data, use of slides and overheads, oral presentation skills, and manuscript preparation and submission. Faculty: Mary Charlson, M.D. 1 credit.

**SAS Data Management and Programming Tutorial.** The SAS tutorial is designed to provide the basic skills necessary to import databases into SAS, and to analyze data. It

covers the use of basic procedures for univariate analyses, using the assist menus, as well as creating simple programs with data transformation. Faculty: TBN. 2 credits.

**Information Skills.** The objective of this course is to provide a knowledge base, skills and techniques for performing literature searches on a variety of search engines including Medline, Ovid, Knowledge Server, and HealthStar. It also provides experience in tracking health-related information from the Internet using several search engines. It provides instruction in quality filters for searches to obtain the most relevant publications. A few sessions of the course are incorporated into the summer curriculum, as a prelude to the more formal course given in the autumn. Both courses focus on building and executing search strategies using Boolean logic and natural language. Participants acquire the skills to broaden or narrow searches and to critically evaluate and quality filter the results by using various search techniques. Faculty: Robert Braude, Ph.D. 2 credits.

**Methods of Clinical Phenomenology and Course of Illness.** This course provides an overview of the research methods used to study psychopathology and comorbid conditions using a longitudinal design. The selection of assessment instruments and statistical approaches appropriate for longitudinal observations are covered. Faculty: George Alexopolous, M.D. 1-2 credits.

**Program Evaluation.** Students learn various techniques for evaluating programs and services, including the type of evaluation required in the context of the program and the population it serves. Students will also learn how to choose a comparison group and learn about options in measuring performance and results. Faculty: William Trochim, Ph.D. 2 credits.

**Clinimetrics: Measurement in Health Research.** The course teaches individuals how to evaluate the purpose of existing measurement scales and their relevance to specific research topics. Question development, item scaling, and overall scale performance are reviewed. Issues pertinent to reproducibility, validation, and responsiveness are also explored. Faculty: Mary E. Charlson, M.D. 2 credits.

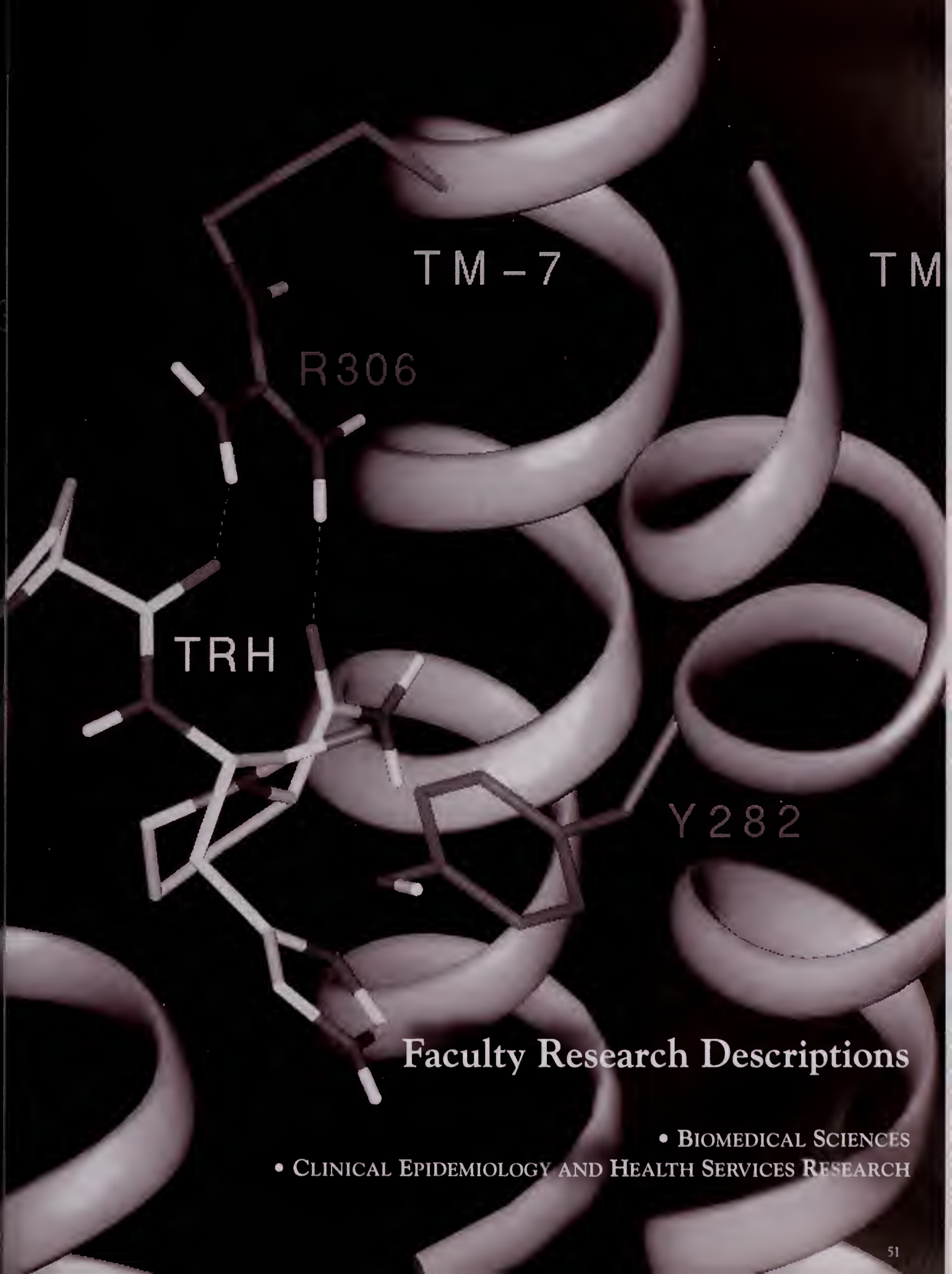
## MULTIDISCIPLINARY CONFERENCES AND COLLOQUIA

The multidisciplinary conferences and seminars focus on important issues in health services research. They are designed to stimulate new interest and involvement in clinical research, create a supportive environment for new clinical and health services research projects, and demonstrate the value of multidisciplinary collaboration. The Health Policy seminars cover a broad range of topics relevant to health policy and involve both CUMC faculty and many distinguished individuals from a broad range of fields in New York and from around the nation.

**Research Methodology Core.** The objective of this course is to review problems with design and conduct of studies. The course operates as "think tank" on issues, and includes a full meeting of a multidisciplinary group consisting of clinical epidemiologists, biostatisticians, health educators, health services researchers, health economists, data systems experts, psychologists, and cooperating investigators.

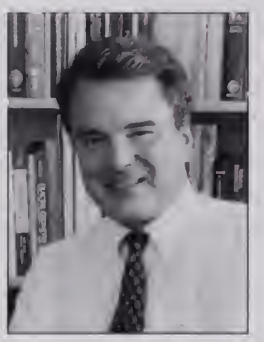
**Laboratory for Clinical Investigation.** The objective of this course is to focus on important issues in health services research. Under the leadership of Dr. Carol Mancuso, the current course is designed to stimulate new interest and involvement in clinical research, create a supportive environment for new clinical and health services research projects, and demonstrate the value of multidisciplinary collaboration.

**David Rogers Health Policy Colloquium.** The objective of this course is to provide broad exposure to the cultural, social, political, and economic issues shaping health policy. Weekly sessions are held with outside speakers from local, state, and national government, as well as with private industry analysts, foundation executives and staff, health policy think tank analysts, academics, and consumer and community interest groups.




# Faculty Research Descriptions

- Biomedical Sciences
- Clinical Epidemiology and Health Services Research



# Olaf S. Andersen, M.D.

## MOLECULAR PHYSIOLOGY OF ION CHANNELS

What determines the folding and therefore the function of membrane proteins? We address these questions using ion conducting channels as an investigative tool. Most experiments are done using channels formed by structurally well-defined antibiotic molecules such as the linear gramicidins; some experiments are done using voltage-dependent ion channels formed by integral membrane proteins.

The gramicidin channels offer a unique combination of advantages that sets them apart from all other ion channels: the channel structure is known at atomic resolution, which guides the experimental design; one can obtain structural information about sequence-modified channels using functional (single-channel) measurements; single-channel measurements provide direct information about the channels' catalytic ability; and gramicidin channels can be used as molecular force transducers to quantify the energetics of channel-membrane interactions.

We use a combination of single-channel experiments, spectroscopic studies and molecular modeling to obtain a molecular understanding of gramicidin channel function. We use this information as a guide for experiments on channels formed by integral membrane proteins. The aim is to understand how the primary amino acid sequence and the anisotropic membrane environment interact in determining the structure and function of membrane-spanning channels. For example, how are the rate of ion movement and the ion selectivity determined by the channel's amino acid sequence and structure. Another aim is to understand how a structural "stress," introduced by sequence modifications, affect the channel dynamics - e.g. how modest sequence alterations introduce voltage control of channel function. Other experiments probe how alterations in the host bilayer alter channel function – specifically how alterations in a bilayer's material properties alter the distribution between different channel states.

We apply this information to explore how alterations in membrane lipid composition, such as those that occur during a coronary occlusion, affect channel gating. We test whether alterations in channel gating can be related to alterations in the host bilayer's material properties through combined studies on channels formed by integral membrane proteins and gramicidin channels.

**RECENT PUBLICATIONS**

**Koeppe, R. E. II and O. S. Andersen. Engineering the gramicidin channel. Annu. Rev. Biophys. Biomol. Struct., 25:231-258, 1996.**

**Nielsen, C., M. Goulian, and O. S. Andersen. Energetics of inclusion-induced bilayer deformations. Biophys. J. 74:1966-1983, 1998.**

*Physiology, Biophysics & Molecular Medicine*

*Biochemistry & Structural Biology*

# Kathryn Anderson, Ph.D.

## DEVELOPMENTAL GENETICS

*Dorsal-ventral patterning in the Drosophila embryo.* In the early Drosophila embryo, cell fate is defined by cell position: ventral cells give rise to mesoderm; lateral cells make the nerve cord and the ventral ectoderm; dorsal cells make dorsal ectoderm. Genetic analysis has revealed that this pattern of cell fates is controlled by an interesting signal transduction pathway. The extracellular steps in the pathway lead to the ventral production of an active ligand (Spätzle) that activates the receptor encoded by the *Toll* gene. The cytoplasmic signaling pathway, which is similar to the mammalian interleukin-1 receptor signaling pathway, leads to nuclear translocation of the Rel-family transcription factor Dorsal. Our goal is to understand the biochemical steps that activate the pathway of the ventral side of the embryo.

*Drosophila immune responses.* The Toll-Dorsal signaling pathway is also important in a very different process, the immune response of the larva and adult. The Drosophila immune response is an evolutionarily conserved process that is similar to the innate immune response of mammals. We have identified nearly 100 mutations that affect specific aspects of the immune response. These mutations define new genes and signaling pathways that are activated in response to infection; we are currently pursuing the genetic and molecular characterization of these pathways.

*Genes controlling mouse embryogenesis.* In contrast to the large number of genes known to control early Drosophila development, the vast majority of genes that control mammalian embryogenesis have not been identified. We are using chemical mutagenesis to identify new genes that regulate early mouse development. Thus far, we have identified 20 mutations that affect a variety of early developmental events, including mesoderm patterning, neural tube closure and heart morphogenesis. We are studying the primary developmental defects in the mutants and will use positional cloning to characterize the most interesting genes molecularly.

**RECENT PUBLICATIONS**

**Wu, L. P. and Anderson, K. V. Regulated nuclear import of Rel proteins in the Drosophila immune response. Nature 392:93-97, 1998.**

**Misra, S., Hecht, P., Maeda, R., and Anderson, K. V. Positive and negative regulation of Easter, a member of the serine protease family that controls dorsal-ventral patterning in the *Drosophila* embryo. Development 125:1261-1267, 1998.**

*Molecular Biology*

# Rosemary F. Bachvarova, Ph.D.

## GASTRULATION OF MOUSE AND CHICK EMBRYOS

The long term goal of my research is the understanding of the molecular control of axis determination and gastrulation of bird and mammalian embryos. We are analyzing the localization of the potential mesoderm inducer activin in and around the pregastrula mouse embryo using immunohistochemistry on sections, and find that it does reach the cavity around the embryo. The effect of the activin inhibitor follistatin on embryos cultured through gastrulation is being examined, and unexpectedly appears to have a relatively mild effect, generally causing posterior defects of the nervous system. We are studying the distribution of apoptotic cells in normal and mutant mouse embryos around the time of gastrulation. Normal embryos have a variable and relatively high rate of cell death which tends to become concentrated in the anterior distal region, the position of the future neutral plate. Mutants being examined include HNF-4 and HNF-3b. In a sabbatical project on chick embryos in the laboratory of Claudio Stern, I have founded a region posterior to the region fated to give rise to the embryo which when transplanted to an anterior half is able to induce a new primitive streak. These experiments may help elucidate the location of the initial differences along the anterior-posterior axis and the site of determinants of the position of the primitive streak.

**RECENT PUBLICATIONS**


**Chen, W.S., Manova, K., Weinstein, D.C., Duncun, S.A., Plump, A.S., Prezioso, V.R., Bachvarova, R.F., and Darnell, J.E. Disruption of the HNF-4 gene, expressed in visceral endoderm, leads to cell death in embryonic ectoderm and impaired gastrulation of mouse embryos. Genes & Dev. 8:2466-2477, 1994.**

**Packer, A.I., Besmer, P. and Bachvarova, R.F. Kit ligand of survival of type A spermatogonia and dividing spermatocytes in postnatal mouse testes. Mol. Reprod. Dev. 42:303-310, 1995.**


*Cell Biology & Genetics*

# Harriet Baker, Ph.D.

## REGULATION OF NEUROTRANSMITTER PHENOTYPIC EXPRESSION, DEVELOPMENT OF PHENOTYPE, NEURONAL PLASTICITY, NEURODEGENERATIVE DISORDERS.

Expression of transmitter phenotype in neurons, both during development and in the adult, results from a number of complex interactions which occur both within and between neurons. To examine these issues my laboratory utilizes the model of afferent regulation of catecholamine gene expression in the olfactory system. Either peripheral afferent denervation or odorant (sensory) deprivation of the olfactory bulb produces profound changes in activity, immunoreactivity and mRNA levels for tyrosine hydroxylase (TH), the first enzyme in the catecholamine biosynthetic pathway and the rate-limiting enzyme in dopamine biosynthesis.

Immunocytochemical, biochemical, northern blot and *in situ* hybridization analyses are employed to further characterize the role of afferent innervation in TH expression. Molecular biological analysis of the TH promoter investigates the process of induction of phenotype in developing animals and mechanisms underlying plasticity of transmitter expression in adults. In addition, phenotypic expression during aging is being studied because olfactory function is compromised both in normal aging and in neurodegenerative syndromes, such as Alzheimer's and Parkinson's diseases. The mechanism for these changes is unknown, but could involve effects primary or secondary to altered afferent innervation. Furthermore, the olfactory system serves as a conduit for entry of some toxins and viruses to the brain. Both the extent and metabolic effects of the entry of xenobiotics into the CNS are pursued in the laboratory.

**RECENT PUBLICATIONS**


**Cho, J.Y., Min, N., Franzen, L. and Baker, H. Rapid down-regulation of tyrosine hydroxylase expression in the olfactory bulb of naris-occluded adult rats. J. Comp. Neurol. 369:264-276, 1996.**

**Moon, Y.W. and Baker, H. Induction of cell division in olfactory basal epithelium following intranasal irrigation with wheat germ agglutinin – horseradish peroxidase. J. Comp. Neurol. 393:472-481, 1998.**


*Neuroscience*

# Francis Barany, Ph.D.

## PROTEIN ENGINEERING AND PROTEIN-DNA RECOGNITION

Human proteins controlling cellular development, gene regulation, and DNA recombination, do so by recognizing specific sequences of DNA. A central question in biology is how proteins recognize DNA in a sequence-specific manner. In this context, *Taq* ligase and *Taq*I endonuclease have served as model systems by virtue of their specificity, ease of production and assay, and thermophilicity. Our approach to studying DNA-protein interactions includes using synthetic templates with novel nucleotide base and backbone analogues, fluorescent assays, electrophoretic mobility shifts, photoaffinity labels, and kinetic analysis. This biochemical approach is complemented by genetic analysis of improved fidelity mutants, "null" mutants, and isoschizomers such as *Tth* HB8I endonuclease. Our genetic analysis may also yield important insights into the elements which contribute to protein thermostability. Ultimately, these results will be correlated with structural determinations on these proteins complexed with DNA using X-ray crystallography and NMR spectroscopy.

Our interest in thermostable DNA recognition proteins has led us into the area of genetic disease detection, which utilizes these proteins for DNA amplification. Using a cloned thermostable ligase, we developed the ligase chain reaction (LCR), which can discriminate a single-base genetic mutation from 10μl blood samples. We are currently combining PCR and LCR for detection of cancer associated mutations as well as genetic diseases. We have focused on two genes, K-*ras* and *p53*, which are among the most commonly mutated in colon and breast cancers. Our laboratory is the lead laboratory of a multi-institutional program project on cancer detection funded by the NCI.

In collaboration with industrial partners, we are developing "DNA chips" for high-throughput analysis of the multiple mutations found in tumors.

Our laboratory employs a wide spectrum of strategies and techniques to study the molecular basis of sequence-specific recognition. These include: Molecular Biology (Automated fluorescent sequencing, library construction, PCR, site-specific mutagenesis, genetic screening); Biochemistry (protein overproduction and purification using FPLC, oligonucleotide synthesis, enzyme kinetics).

**RECENT PUBLICATIONS**


**Luo, J. Bergstrom, D., and Barany, F. Improving the fidelity of *Thermus thermophilus* DNA ligase. Nucleic Acids Research 24:3071-3078, 1996.**

**Cao, W., Lu, J., and Barany, F. Nucleotide sequences and gene organization of *Taq*I endonuclease isoschizomers from *Thermus sp.* SM32 and *Thermus filiformis* Tok6A1. Gene 197:205-214, 1997.**


*Molecular Biology*

*Biochemistry & Structural Biology*

# Craig T. Basson, M.D., Ph.D.

## MOLECULAR GENETICS OF CARDIOVASCULAR DEVELOPMENT

To identify novel genes that regulate cardiac differentiation and morphogenesis, we have applied molecular genetic techniques to congenital and inherited disorders of human cardiac growth and development.

1. Congenital cardiac and upper limb malformations characterize the autosomal dominant disorder Holt-Oram syndrome. Our genetic analyses mapped the Holt-Oram gene to human chromosome 12q24.1 and identified TBX5, a novel human T-box transcription factor. Sequence analysis demonstratd a variety of mutations in this gene which cause Holt-Oram syndrome. Ongoing correlation of TBX5 genotypes with Holt-Oram phenotypes suggests that TBX5 mutations produce a combination of severe limb and severe cardiac malformation through both haploinsufficiency and steric hindrance at DNA binding sites. In vitro studies are currently exploring the effects of mutant and wildtype TBX on cardiomyocyte differentiation. In addition, we are establishing animal models of aberrant TBX5 expression, including overexpression of wildtype and mutant TBX5 isoforms in the embryonic chicken heart.

2. Intracardiac tumors, including atrial myxomas, are significant causes of stroke and heart failure and may present as heritable systemic disorders. The Carney complex is an autosomal dominant syndrome in which intracardiac myxomas arise in the setting of cutaneous hyperpigmentation and endocrinopathy. Our molecular genetic analyses have defined a novel chromosomal locus that contains the Carney complex disease gene in several families. Current positional cloning efforts and loss of heterozygosity analyses seek to identify the mutations in the novel gene at this locus that cause intracardiac myxomas. Resultant increased understanding of the regulation of cardiac cell growth will improve management of intracardiac myxomas and will also suggest novel approaches to stimulate cardiac remodeling that can contribute to the treatment of the myopathic and ischemic heart.

3. Similar molecular genetic studies seek to identify disease genes related to isolated cardiac septal defects, abnormal atrioventricular valve formation, and malformations fo the aortic outflow tract.

**RECENT PUBLICATIONS**


**Basson, C.T., MacRae, C.A., Korf, B., Merliss, A. Genetic heterogeneity of familial atrial myxoma syndromes. Amer. J. Cardiology 79(7):994-995, 1997.**

**Basson, C.T., Bachinsky, D.R., Lin, R.C., Levi, T., Elkins, J., Soults, J., Grayzel, D., Kroumpouzou, E., Traill, T.A., LeBlance-Straceski, J., Renault, B., Kucherlapati, R. Seidman, J.G., Seidman, C.E. Holt-Oram syndrome. Nature Genetics 15:30-35, 1997.**


*Cell Biology & Genetics*

# Mary Baylies, Ph.D.

## MOLECULAR MECHANISMS OF DEVELOPMENT

How does a group of cells integrate the information in its environment and commit to a particular developmental fate? We address this question by focusing on the underlying mechanisms involved in mesodermal patterning and myogenesis in the fruit fly, *Drosophila melanogaster*. The mesoderm gives rise to a number of distinct cell types, such as somatic muscles, heart, visceral muscles and fat body. Our results show that levels of the basic-helix-loop-helix transcription factor, Twist, are a critical determinant of cell fates in the mesoderm. For example, we find that cells with high levels of Twist form somatic muscles whereas cells with lower levels of Twist are able to form other mesodermal tissues such as visceral muscles and heart. Furthermore, four signal transduction pathways — Wingless, Decapentaplegic, Notch and Ras — are required for segregation and differentiation of somatic, heart and visceral muscles. By using a combination of molecular, cellular, genetic and biochemical techniques, we are investigating : 1) how Twist performs its role at key mesodermal decision points throughout development. Our current hypothesis is that specific dimerization partners regulate Twist activity; 2) how levels of Twist are set up. We are investigating sites within the *twist* promoter that are potential targets for signal transduction pathways; 3) how cells integrate the information that they receive in time and space. We are testing whether the signal transduction pathways and Twist achieve different outcomes at different points in development through alterations in the association of critical transcription regulators; and 4) what elements of the myogenic program (Twist, signals) have been conserved between Drosophila and vertebrate systems. Our goal is to use the pivotal role that Twist plays in mesodermal development to understand the mechanisms that drive the diversification and patterning of this group of cells in flies and vertebrates.

**RECENT PUBLICATIONS**


**Baylies, M.K. and Bate, M. *twist*: a Myogenic switch in *Drosophila*. Science 272:1481-1484, 1996.**

**Baylies, M.K., Bate, M., and Ruiz Gomez, M. Myogenesis: A View from Drosophila. Cell (in press).**


*Molecular Biology*

# M. Flint Beal, M.D.

## NEUROCHEMISTRY LABORATORY

The research in our laboratory investigates fundamental mechanisms of cell death in neurodegenerative diseases. We have principally focused on the role of mitochondrial dysfunction and oxidative damage in neurodegenerative diseases. Our studies have utilized cell culture models, transgenic animal models, mitochondrial toxin animal models, postmortem neurochemical studies, studies of oxidative damage markers in body fluids of patients, and MRI spectroscopy. Our laboratory has developed a large number of sensitive and specific biochemical assays for markers of oxidative damage. We have also developed techniques to measure a large number of energy related metabolites. These techniques have been utilized to investigate transgenic and other animal models with relevance to Huntington's disease, amyotrophic lateral sclerosis, Parkinson's disease and Alzheimer's disease. We have also investigated a number of novel therapeutic interventions related to attempts to buffer intracellular energy stores and to prevent oxidative damage.

**RECENT PUBLICATIONS**


**Matthews, R.T., Yang, L., Browne, S., Bail, M., Beal, M.F. Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. Proc. Natl. Acad. Sci. USA 95: 8892-8897, 1998.**

**Matthews, R.T., Yang, L., Jenkins, B.G., Ferrante, R.J., Rosen, B.R., Kaddurah-Daouk ,R., Beal, M.F. Neuroprotective effects of creatine and cyclocreatine in animal models of Huntington's Disease. J. Neurosci. 18:156-163, 1998.**


*Neuroscience*

# Robert Benezra, Ph.D.

## MOLECULAR MECHANISMS OF DIFFERENTIATION AND MITOTIC CHECKPOINT CONTROL

One of the primary goals of the laboratory is to elucidate the molecular mechanisms of differentiation in mammalian cells. Our research is centered on the genetic and biochemical characterization of a protein that we have identified called Id (for "Inhibitor of differentiation"), that appears to antagonize the action of a class of transcription factors involved in cell-fate determination. Most notably, Id inhibits the muscle-regulatory gene MyoD from activating the muscle differentiation program in mouse cells by direct protein-protein interactions.

We have initiated a genetic analysis of the role of the Id proteins in mouse development. Disruption of two related Id proteins (Id1 and Id3) in mice leads to the death of the animal at about embryonic day 12.5 with evidence for premature differentiation in neural as well as hematopoietic cell lineages. In addition, expression of the Id genes appears to be required for the growth of endothelial cells that takes place during the vascularization of tumors. Current efforts are directed at defining precisely the cellular and biochemical consequences of the loss of the Id proteins in these affected cell lineages.

Another area of interest in the laboratory is the analysis of the first mitotic checkpoint gene identified in humans, hsMAD2. We have shown that hsMAD2 is required for cells to arrest in mitosis if the mitotic spindle assembly is perturbed. Such perturbations may occur during normal somatic cell division and lead to the chromosome instability in the absence of MAD2. Since chromosome instability is one hallmark of tumor progression, MAD2 is predicted to be a tumor suppressor gene, a hypothesis that is currently being tested by the generation of MAD2 null mice and the analysis of human tumor cell samples. In addition, we are studying the biochemical mechanism of MAD2 activity by an analysis of the interaction of MAD2 with components of the ubiquitin-proteosome pathway, a pathway required for the execution of the metaphase to anaphase transition in eukaryotic cells.

**RECENT PUBLICATIONS**


**Yan, W., Young, A.Z., Soares, V.C., Kelley, R., Benezra, R. and Zhuang, Y. High incidence of T-cell tumors in E2A null mice and E2A/Id1 double knockout mice. Mol. Cell Biol. 17:7317-7327, 1997.**

**Li, Y., Gorbea, C., Mahaffey, D., Rechsteiner, M. and Benezra, R. MAD2 associates with the cyclosome/anaphase-promoting complex and inhibits its activity. PNAS, USA 94:12431-12436, 1997.**


*Cell Biology & Genetics*

# Leif Bergsagel, M.D.

## THE MOLECULAR PATHOGENESIS OF MYELOMA

Multiple myeloma (MM) is a tumor of mature, isotype-switched plasma cells. It is a uniformly fatal malignancy that is frequently preceded by a common (1% of adults), benign pre-clinical phase, monoclonal gammopathy of undetermined significance (MGUS). Our laboratory is focused on understanding the molecular events that lead to the development of MGUS, and to its progression to MM. In the last couple of years we have determined that MM is characterized by recurrent chromosome translocations to the immunoglobulin heavy chain gene on 14q32. We have identified three frequent translocation partners, that each occurs in about 20-25% of MM, and several infrequent ones.

We have cloned four translocation breakpoints on 11q13, from 50-300kb upstream of cyclin D1, associated with the ectopic expression and dysregulation of cyclin D1 mRNA and protein. We have cloned 5 translocation breakpoints on 4p16.3, from 50-120kb upstream of fibroblast growth factor receptor 3 (FGFR3). The t(4;14) is a novel, karyotypically silent translocation associated with the ectopic expression and dysregulation of FGFR3 mRNA and protein. Most recently we have cloned 4 translocation breakpoints on 16q23, within approximately 500 kb of c-maf. The t(14;16) is also a novel, karyotypically silent translocation that is associated with the ectopic expression and dysregulation of c-maf mRNA. C-maf is the first basic zipper transcription factor to be directly implicated in tumorigenesis in man. Finally using genomic sequence analysis and computer cloning we have identified and cloned a novel trithorax homologue that is dysregulated by hybrid mRNA transcripts with the IgH locus.

Using murine and *in vitro* models, we are studying how cyclin D1, FGFR3 and c-maf contribute to the development of multiple myeloma, and continuing our analysis and cloning of novel translocation breakpoints and oncogenes.

**RECENT PUBLICATIONS**


**Chesi, M., Nardini, E., Brents, L.A., Schrock, E., Ried, T., Kuehl, W.M., Bergsagel, P.L. Frequent translocation t(4;14)(p16.3;q32.3) in multiple myeloma is associated with increased expression and activating mutations of fibroblast growth factor receptor 3. Nature Genetics 16: 260, 1997.**

**Chesi, M., Bergsagel, P.L., Shonukan, O.O., Martelli, M.L., Brents, L.A., Chen, T., Schrock, E., Ried, T., Kuehl, W.M. Frequent dysregulation of the c-maf protooncogene at 16q23 by translocation to an immunoglobulin locus in multiple myeloma. Blood (June 15) 1998, in press.**


*Immunology*

# Joseph R. Bertino, M.D.

## MOLECULAR PHARMACOLOGY

The focus of this laboratory is to understand the basis of intrinsic and acquired resistance to drugs, and to develop new therapies or approaches to cancer treatment based on this information. Cell lines and tumors from patients are studied to determine the basis of drug resistance and sensitivity to antimeta-bolites, in particular folate analogs, and fluoropyrimidines. The role of oncogenes and tumor suppressor genes is being explored in relation to drug resistance.

A related effort in this laboratory is the development and use of retroviral vectors to transfer drug resistance genes into bone marrow hematopoietic precursor cells. The drug resistance genes employed are dihydrofolate reductase and thymidylate synthase, targets for methotrexate and tomudex, respectively. By site directed mutagenesis, mutant forms are generated for use in these studies, and tested in the mouse model. In collaboration with Drs. Michel Sadelain (Human Genetics) and Malcolm Moore (Cell Biology Program), these genes are introduced into hematopoietic progenitor cells (CD 34+) from bone marrow and peripheral blood. The eventual goal of these studies is to use these drug resistance genes to impart resistance of normal hematopoietic progenitor cells to drugs, thus allowing larger doses of the desired drug to be utilized for therapy. A second aim of these studies is to use these drug resistance genes as selectable markers that will allow persistence and expression of a non-selectable gene.

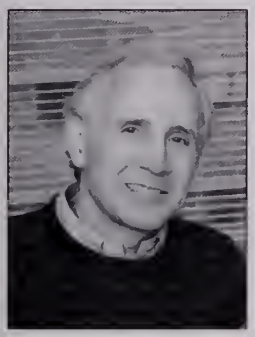
Parallel to these studies, the regulation of dihydrofolate reductase and thymidylate synthase, target enzymes for antifolate chemotherapeutic agents, is being studied at both the transcriptional and translational level, with the goal toward developing agents that interfere with these processes.

**RECENT PUBLICATIONS**


**Abali-Ercikan, E.A., Banerjee, D., Waltham, M.C., Skacel, N., Scotto, K.W., and Bertino, J.R. Dihydrofolate reductase protein inhibits its own translation by binding to dihydrofolate reductase mRNA sequences within the coding region. Biochemistry 36(40):12317-12322, 1997.**

**Tong, Y., Chen-Liu, X., Abali-Ercikan, E.A., Zhao, S-C., Banerjee, D., and Bertino, J.R. Isolation and characterization of thymitaq (AG337) and fluorodeoxyuridine (FdUrd)-resistant mutants of human thymidylate synthase from ethylmethanesulfonate-exposed human sarcoma HT1080 cells. J. Biol. Chem. 273:11611-11618, 1998.**


*Pharmacology*



# Peter Besmer, Ph.D.

## SIGNAL TRANSDUCTION AND DEVELOPMENT

Receptor tyrosine kinases (RTK) and their ligands transmit extracellular signals to target cells and they control cellular processes such as proliferation, survival, motility, secretion, and differentiation. RTK's play key roles in embryonic development, in organogenesis, and in the adult life of invertebrate and vertebrate animals. Quite often RTKs are expressed and function in several distinctive cell types where they may exhibit pleiotropic roles. In part this pleiotropism may be the result of the different cellular context in which the receptors are functioning. Understanding the basis of cell type specific signaling is an important current line of investigation. A major effort in this laboratory is to understand mechanisms by which pleiotropic responses of RT's are controlled and as a model for this Kit ligand (KL) and its cognate receptor the Kit RTK is being studied. The Kit RTK is encoded at the White Spotting locus in the mouse and KL at the Steel locus. Mutations at the murine *W* and *Sl* loci generate deficiencies in several major cell systems during embryogenesis and in the postnatal animal including hematopoiesis, the pigmentary system, intestinal pacemaker cells, and in gametogenesis.

KL is a membrane growth factor which may be processed to produce soluble KL. KL may function both as a soluble and as a membrane factor. Thus, the investigation of the respective roles of soluble and membrane-associated factors is of great interest. The laboratory is interested to determine the mechanisms by which soluble KL is produced and to elucidate the respective roles of soluble and membrane-associated KL *in vivo* during embryonic development and in the postnatal animal. Biochemical and genetic approaches *in vivo* are being used in these studies. The effects of germline modifications in the KL gene on hematopoiesis are being investigated in collaboration with Dr. Moore's laboratory (Program of Cell Biology and Genetics).

RTKs such as Kit activate several cellular signaling cascades through the phosphorylation of various substrates and the association with signaling molecules. An important goal in the laboratory is the elucidation of the mechanism by which the Kit RTK mediates various cellular responses in *in vitro* cell systems and *in vivo*. As a cell model for the investigation of the mechanism of Kit receptor signaling mast cells are being used. In mast cells cellular responses which are mediated by Kit include cell proliferation, cell survival, cell adhesion, and secretion. To study the mechanism of Kit signaling in various cell systems *in vivo*, we are generating mice carrying Kit-receptor mutations which affect distinct signaling pathways by modifying the Kit gene in the germline by knock-in technology. Analysis of mice carrying these mutations will provide insight about the mechanism of Kit signaling in various cell systems including hematopoiesis, gametogenesis, and melanogenesis.

**RECENT PUBLICATIONS**


**Vosseller, K., Stella, G, Yee, N., and Besmer, P. C-kit receptor signaling through PI-3 kinase and protein kinase C: Role in mast cell – enhancement of degranulation, adhesion and membrane ruffling. Mol. Biol. Cell 8:909-922, 1997.**

**Tajima, Y., Huang, E.J., Vosseller, K., Ono, M., Moore, M.A.S., and Besmer, P. Role of dimerization of the membrane associated growth factor KL in juxtacrine signaling: the Sl17h mutation affects dimerization and stability - phenotypes in hematopoiesis. J. Exp. Med. 187 (in press) 1998.**


*Molecular Biology*

# Thomas J. J. Blanck, M.D., Ph.D.

## VOLATILE ANESTHETIC ACTIONS

Although the volatile anesthetics (VA) are administered to over 100,000,000 people per year, the mechanism of action of these halogenated hydrocarbons is unknown. Because a common side effect of the VA is depression of cardiac contractile activity, our lab has examined the mechanism of this depression as a model for VA action in general. It has been shown that the VA interfere with $Ca^{2+}$- regulation in the myocardial cell. We have demonstrated an interference by the VA with L-type voltage dependant $Ca^{2+}$- (VDCC) antagonist binding. This has been described *in vitro* in cardiac membranes isolated from rat, rabbit, bovine, and human myocardium, and we have recently demonstrated that this phenomenon also occurs in the intact perfused heart.

The VA have also been shown to facilitate opening of the calcium release channel (CRC) of the sarcoplasmic reticulum (SR) of muscle. At this time the data suggest that there is little alteration by the VA of the SR $Ca^{2+}$- pump and of the interaction of $Ca^{2+}$- with the myofibrilla regulatory protein, troponin C (TnC). At present no evidence exists as to the effect of the VA on the Na+ -Ca2+ exchange.

Based on these data, we propose a model for VA action. In this model, the VA directly depress contractility by inhibiting the entry of $Ca^{2+}$- through the VDCC. The decreased $Ca^{2+}$- stimulates a decreased $Ca^{2+}$- -induced $Ca^{2+}$- release from the SR, but since the CRC is sensitized by the VA, over time the total SR $Ca^{2+}$- decreases, leading to a steady state decrease in total cell $Ca^{2+}$-. This hypothesis requires that the $Na^{+}$-$Ca^{2+}$ exchange is minimally affected, so that there is a net loss of $Ca^{2+}$- from the cell.

This laboratory has recently extended observations on the effect of VA to the CNS, and to ischemic effects on myocardial and CNS tissue. $Ca^{2+}$- homeostasis is altered in these situations as well and the VA are major effectors in modifying the $Ca^{2+}$- homeostatic mechanisms.

**RECENT PUBLICATIONS**


**Sarti, P., Paroli, L., Blanck, T.J.J. Effect of exogenous cytochrome C on respiratory activity of rat heart myocytes undergoing cell death. Biophysical Journal A17:M-AM-G1, 1998.**

**Haile, M., Heerdt, P., Kang, R., Blanck, T.J.J. Isoflurane does not improve return of myocardial function after global ischemia in dogs. Abstracts, Anesth Analg 86-S66, 1998.**


*Physiology, Biophysics & Molecular Medicine*

# Ronald G. Blasberg, M.D.

## POSITRON EMISSION TOMOGRAPHY AND GENE IMAGING RESEARCH

A PET research program has been in existence at MSKCC since the early 1980s and is currently being upgraded with new facilities to include a state of the art G.E. advanced tomograph and a new cyclotron. There is a basic research and a clinical research program. The basic research program develops and validates new tracer-imaging methodologies (e.g., tumor cell proliferation, up-regulation of amino acid transporters in tumors, the expression of transduced foreign genes), and develops new image analysis techniques. *In vitro* studies in tissue culture and biodistribution studies in animals using multi-isotope quantitative autoradiography are performed. A goal of the basic program is to complement the PET research program; thus, much of the clinical program evolves out of the basic research program. Functional brain imaging is also being developed. Brain activation "maps" to specific stimuli will be obtained in normal and pathologic brain, and will provide new insights into cognitive and other mental processes in normal subjects and in specific disease states. Other research projects will involve measurements of opiate receptor density and the binding of opiate agonists in normal and chronic pain states.

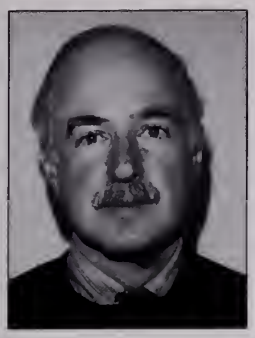
The gene imaging program is being pursued by interacting with several groups within the Departments of Neurology and Human Genetics, the Nuclear Medicine Service, and the Molecular Pharmacology and Experimental Therapeutics Program at MSKCC. We have demonstrated "proof of principle" by imaging HSV1-tk gene expression with radiolabeled FIAU, and we are evaluating other potential marker gene-marker substrate combinations. A current focus is to develop and evaluate different multigene expression cassettes for stable and proportional coexpression of two genes, such that one could be used as a marker gene (e.g., HSV1-tk) to monitor the expression of the second (therapeutic) gene. Our group is also comparing different gene delivery vectors, including retrovirus, adenovirus, and mutant herpes virus. A long range goal is to combine gene imaging with novel gene-therapy paradigms that have potential patient applications.

**RECENT PUBLICATIONS**


**Tjuvajev, J., Stockhammer, G., Desai, R., Uehara, H., Watanabe, K., Gansbacher, B., Blasberg, R. Imaging expression of transfected genes *in vivo*. Cancer Research 55: 6126-6132, 1995.**

**Tjuvajev, J.G., Finn, R., Watanabe, K., Joshi, R., Oku, T., Kennedy, J., Beattie, B., Koutcher, J., Larson, S., Blasberg, R.G. Noninvasive Imaging of Herpes Virus Thymidine Kinase Gene Transfer and Expression: A Potential Method for Monitoring Clinical Gene Therapy. Cancer Research 56:4087-4095, 1996.**


*Neuroscience*



# John Blass, M.D., Ph.D.

## MOLECULAR AND BIOCHEMICAL MECHANISMS IN DISEASES OF THE NERVOUS SYSTEM

My particular interest has been in identifying biochemical and genetic abnormalities in patients with specific diseases and then studying how the abnormality in the molecule contributes to the clinical manifestations of the disease. I was part of the team that characterized the defect in Refsum's Disease. I described the first inborn error in the quantitatively major pathways of energy metabolism, namely pyruvate dehydrogenase (PDHC) deficiency; this is now a well known and well studied inborn error, which includes the majority of cases of the subacute necrotizing encephalopathy of Leigh. We described the existence of an abnormality in a specific thiamin pyrophosphate dependent enzyme, transketolase, in a form of thiamin deficiency affecting the nervous system (Wernicke-Korsakoff Syndrome). The existence of such a defect has been extensively confirmed, although the molecular basis is still not worked out. My coworkers and I demonstrated the existence of mitochondrial abnormalities in many patients with hereditary ataxias, including a subgroup of patients with PDHC deficiency.

Recently colleagues and I have concentrated on degenerative neurological diseases of aging and particularly on Alzheimer's disease. We are closely identified with a hypothesis that there is an inherent mitochondrial defect in this disorder, with our most recent publication on this subject appearing in the Annals of Neurology in 1994 and our most recent review in Neurology in 1993. The existence of such a defect, as demonstrated by confirmations of our studies on 2 mitochondrial multienzyme complexes (PDHC and KGDHC) is widely acknowledged, but the pathophysiological significance is still debated. Recent work by my colleagues and myself, in collaboration with coworkers at Harvard, has led to cloning of the cDNA for one candidate gene (E2k of KGDHC) and discovery of evidence for polymorphic markers associated with AD for 2 of the KGDHC proteins, E1k and E3.

The other major area with which I and my colleagues are identified is the use of non-neural cells (notably cultured skin fibroblasts) to study molecules which are identical in brain and non-neural cells, and processes which these molecules catalyze. More recently, we have been studying "fibroblasts" cultured from cerebral tissues. These cells, when cultured under defined conditions, contain neuronal marker proteins (NSE and neurofilaments) and make processes. Transplantation of these cells is being studied; results to date with fast blue raise the possibility that these "fibroblasts" may be neural precursor cells.

**RECENT PUBLICATIONS**


**Kurita, A., Black, R.S., Nolan, K.A. and Blass, J.P. (1993) Dementia of the vascular type with normal CT scan. J. Geriat. Neurol. Psychiat., in press.**

**Jung E-H., Sheu K-F.R., and Blass, J.P. (1993) An enzymatic and immunochemical analysis of transketolase in fibroblasts from Wernicke-Korsakoff syndrome. J Neurol Sci 114:123-127.**


*Neuroscience*

# Carl P. Blobel, M.D., Ph.D.

## METALLOPROTEASE-DISINTEGRIN PROTEINS

The research in my lab is focused on metalloprotease-disintegrin proteins, a recently discovered family of membrane anchored glycoproteins which are related to snake venom metalloproteases and integrin ligands. Metalloprotease-disintegrins are known to mediate important and diverse biological processes, such as sperm-egg membrane binding and fusion, myoblast fusion, neuronal development and neurite migration, and the release of the membrane anchored cytokine TNF from the plasma membrane.

The first recognized metalloprotease-disintegrin was the sperm protein fertilin, which is thought to bind to an integrin-type receptor on the egg. A few years ago, my lab was the first to demonstrate that metalloprotease-disintegrins are a protein family, and currently more than 25 members of this protein family are known to exist. We are now concentrating our efforts on two metalloprotease-disintegrins, termed MDC9 and MDC15, as model proteins to further our understanding of the structure and function of MDC proteins.

Specifically, we are: a) evaluating the protease activity and substrate specificity of the expressed metalloprotease domains of MDC9 and MDC15, b) studying the ability of the expressed disintegrin domain of both proteins to bind to integrins and to promote cell adhesion, and c) characterizing the role of cytoplasmic proteins in regulating the function of MDC9 and MDC15. Furthermore, we have generated targeted deletions of MDC9 and MDC15 in mice in order to study the function of these two MDC proteins during mouse development and in the adult animal.

**RECENT PUBLICATIONS**


**Weskamp, G., Kratzschmar, J., Reid, M. and Blobel, C.P. MDC9, a widely expressed cellular disintegrin containing cytoplasmic SH3 ligand domains. J.Cell Biol. 132:717-726, 1996.**

**Blobel, C.P. Metalloprotease-disintegrins:Links to cell adhesion and cleavage of TNF and Notch. Cell 90:589-592, 1997.**


*Cell Biology & Genetics*

# Adele L. Boskey, Ph.D.

## MECHANISM OF BIOLOGICAL CALCIFICATION

Physiologic calcification in mammals involves calcium phosphate apatite crystal deposition within the extracellular matrices of bones, teeth, ligaments, and tendons. The process of physiologic calcification is critical to the mechanical functions of the body as well as to the maintenance of calcium homeostasis. The precise mechanisms which determine where mineral is deposited, when mineral forms, and what regulates the growth of mineral crystals, is the subject of investigators in our laboratory. Such studies are conducted using solution, cell culture, and *in vivo* models.

The effects of individual native- or chemically- modified proteins on the formation (nucleation) and growth of apatite crystals are studied in solution in a gelatin gel. With these systems we have identified several non-collagenous matrix proteins, in particular phosphoproteins, which can both nucleate apatite mineral crystals and regulate the size and shape of these crystals.

In cell cultures, modification of matrix protein expression is used to confirm mechanisms suggested from studies with isolated proteins. Protein expression is regulated at the translational and post-translational levels, or by variation of mechanical force. Analysis of mineral properties is achieved through x-ray diffraction, transmission electron microscopy, and Fourier Transform Infrared Microspectroscopy (FTIRM). FTIRM has been developed in our laboratory as a quantitative technique for determining apatite mineral crystal composition, size, and perfection at the light microscopic level.

FTIRM is also used to characterize mineral and matrix changes in osteoporosis in an effort to understand the etiology of this disease, and the effects of current therapies on the quality of the bone. Combined with mechanical studies, FTIRM is used to elucidate the effect of matrix proteins on whole bone properties - studying naturally occurring mutants, transgenic, and knockout animals. These studies combine to provide new insights into the way calcified tissues form in health and disease.

**RECENT PUBLICATIONS**


**Paschalis, E.P., DiCarlo, E., Betts, F., Sherman, P., Mendelsohn, R., and Boskey, A.L.: FTIR Microscopic Analysis of Human Osteonal Bone. Calcif Tissue Intl 59:480-487, 1996.**

**Boskey AL, Spevak M, Doty S, Rosenberg L: Effects of Bone Proteoglycans, Decorin and Biglycan on Hydroxyapatite Formation in a Gelatin Gel. Calcif Tissue Int. 61:298-305, 1997.**


*Biochemistry & Structural Biology*

# Patrick J. Brennwald, Ph.D.

## MOLECULAR GENETIC ANALYSIS OF INTRACELLULAR VESICLE TRANSPORT

Intracellular movement of proteins within and their release outside of eukaryotic cells is a process that is critical to a wide variety of biological functions and defects in this process have been linked to a number of human diseases. The intracellular trafficking of proteins from one compartment to another is thought to be mediated by transport vesicles which bud off one compartment and are then targeted to fuse specifically with a second compartment. Recent work has implicated a set of proteins, known as the SNARE complex, in the targeting and/or fusion of synaptic vesicles with the plasma membrane during neuronal exocytosis. We have identified and extensively characterized a very similar complex from budding yeast which is also required for exocytosis. Our genetic and biochemical analysis of this complex has led us to the identification of a new regulatory pathway involving a Rho GTPase and a pair of novel Sec9 binding proteins which are required for normal growth and exocytosis in yeast. Currently my laboratory is pursuing several avenues related to the function of these proteins in polarized exocytosis: 1) We are examining the role of two Sec9 binding proteins, Sni1 and Sni2, in regulating the function of the SNAP-25 homolog, Sec9. 2) We are studying the role of the Rho GTPase, Rho3, in exocytosis as well as an upstream activator of Sni1/2. 3) We are examining the role of both Rho3 and Sni1/2 in polarized exocytosis and polarized actin assembly. 4) Finally we are testing the model that Rho3/Sni1/Sec9 pathway is conserved in higher eukaryotic cells which may involve members of a family of proteins which includes the Drosophila tumor suppressor gene lethal giant larvae. These studies will have important implications in both understanding the function of Rho GTPases in exocytosis as well as in unraveling a novel mechanism for regulation of t-SNARE function at the plasma membrane. This regulation may represent a key mechanism by which eukaryotic cells regulate and coordinate the polarity of the actin cytoskeleton with the polarized release of substance outside the cell.

**RECENT PUBLICATIONS**


**Rossi, G., Salminen, A., Rice, L.R., Brnger, A. T., and Brennwald, P. Analysis of a Yeast SNARE Complex Reveals Remarkable Similarity to the Neuronal SNARE Complex and a Novel Function For the C-terminus of the SNAP-25 Homolog, Sec9. J. Biol. Chem. 272, 16610-16617, 1997.**

**Katz, L., Heuser, J., Hanson, P., Brennwald, P. Genetic and Morphological Analysis Reveals a Critical Interaction between the C-termini of two SNARE proteins and a Parallel Four Helical Arrangement for the Exocytic SNARE Complex. EMBO J. 17:6200-6209, 1998.**


*Cell Biology & Genetics*

# Esther M. Breslow, Ph.D.

## PROTEIN FOLDING AND INTERACTIONS

Our principal interest is the analysis of interrelationships among protein primary structure, folding and biological recognition. We have largely focused on the structure of a single small pituitary protein, neurophysin, analyzing, in thermodynamic and molecular detail, its interactions with the peptide hormones oxytocin and vasopressin and the complex processes that regulate its dimerization and folding. Neurophysin serves as a carrier for the hormones within the pituitary and shares common biosynthetic precursors with the hormones. Mutations in neurophysin are associated with defects in vasopressin production and the disease diabetes insipidus.

Examples of our current research:

1. *What factors influence protein dimerization?* Protein self-association plays important biological roles in normal and pathological states, but conformational factors modulating self-association are inadequately understood. In the case of neurophysin, dimerization is markedly altered by events distant from the monomer-monomer interface, such as hormone-binding. We are exploring the mechanisms involved, using a combination of crystallographic and NMR approaches.

2. *How do multi-domain proteins fold?* Neurophysin contains two homologous domains that interact in the folded state. The extent to which folding is dependent on interdomain interactions is being studied by comparison of the folding of the whole protein with that of isolated domains. Neurophysin contains 7 disulfide bridges per chain. The ability to correctly pair these disulfides within the isolated domains is a particular focus of investigation.

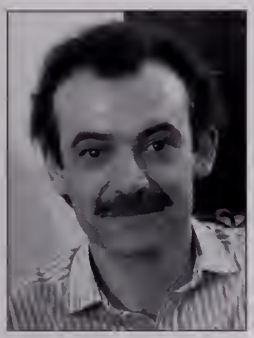
3. *How do mutations in neurophysin lead to defects in vasopressin production?* The importance of neurophysin to hormone production lies in the correct targeting of hormone to regulated neurosecretory granules. The nature of this role, and the mechanism by which mutations impair neurophysin function, are under investigation.

**RECENT PUBLICATIONS**


**Deeb, R. and Breslow, E. Thermodynamic role of the pro region of the neurophysin precursor in neurophysin folding: evidence from the effects of ligand peptides on folding. Biochemistry 35:864-873, 1996.**

**Rose, J.P., Wu, C.-D., Breslow, E. and Wang, B.-C. Crystal structure of the neurophysin-oxytocin complex. Nat. Struct. Biol. 3:163-169, 1996.**


*Biochemistry & Structural Biology*



# Anthony M. C. Brown, Ph.D.

## WNT SIGNALING AND CANCER

Wnt proteins constitute a family of 18 or more secreted proteins that act as extracellular signaling factors. They function in cell-fate determination and patterning in embryogenesis, and in the regulation of cell growth and differentiation in a variety of organ systems. *Wnt* genes were first discovered as mammary oncogenes in the mouse, and aberrant activation of the Wnt signaling pathway is associated with precancerous conditions in other tissues.

Research in the laboratory centers on the mechanism of action of Wnt proteins, the intracellular signaling pathway through which they act, their phenotypic effects on target cells, and their functions in normal development and tumorigenesis. Candidate cell surface receptors for Wnt proteins have recently been identified and we are investigating their functions, focusing on those expressed in mammary cells. We are using soluble biologically active forms of Wnt proteins to characterize ligand-receptor interactions and to investigate the specificity of action of different members of the Wnt family. Intracellular signaling pathways activated by Wnt proteins are also under investigation. Wnt signals act via a novel pathway that includes proteins of the Dishevelled family and leads to stabilization of β-catenin and plakoglobin. β-catenin is of particular interest because it plays a structural role in cell-cell adhesive junctions, yet is also able to enter the nucleus and modulate transcription.

Overexpression of *WNT* genes has recently been observed in both breast and colon cancer in humans. In addition, the tumor suppressor gene APC, which is mutated in the majority of colorectal cancers, encodes a negative modulator of intracellular Wnt signaling. These and other data suggest that the Wnt signaling pathway may be of widespread significance for early stage cancer in several tissues. In collaboration with colleagues at the Strang Cancer Prevention Center we are therefore investigating the role of this pathway in human cancer.

**RECENT PUBLICATIONS**


**Bradley, R.S., and Brown, A.M.C. A soluble form of Wnt-1 protein with mitogenic activity on mammary epithelial cells. Mol. Cell. Biol., 15, 4616-4622, 1995.**

**Shimizu, H., Julius, M.A., Giarré, M., Zheng, Z., Brown, A.M.C., and Kitajewski, J. Transformation by Wnt family proteins correlates with regulation of β-catenin. Cell Growth Differ. 8, 1349-1358, 1997.**


*Cell Biology & Genetics*

*Molecular Biology*

# Jochen Buck, M.D., Ph.D.

## RETRO-RETINOIDS: A NEW CLASS OF INTRACELLULAR MESSENGER MOLECULES

Activation and proliferation of lymphocytes and fibroblasts are critically dependent on a source of vitamin A. In its absence, cells die within 2-7 days. Retinol, but not retinoic acid, supports the survival of these cells demonstrating that transcriptional activation via retinoic acid receptors is not the only signaling pathway emanating from vitamin A.

Our work on this alternative signaling pathway led to the discovery of two new intracellular messenger molecules starting from the common precursor retinol. Activated lymphocytes and most other cell lines produce 14-hydroxy-retro-retinol (14-HRR) which mediates the growth supporting activity of vitamin A. The second physiological retinol derivative, anhydroretinol (AR), is a competitive antagonist of 14-HRR and induces rapid cell death in vitamin A dependent cells. We continue to study these retroretinoids and their signal transduction mechanisms. Of utmost importance is the purification and cloning of cellular 14-HRR/AR binding proteins/receptors which contribute to their growth modulatory activities.

Recently, we purified and cloned the enzyme producing anhydroretinol. This is the first example of an enzyme able to utilize free retinol at physiological intracellular concentrations. Using the knowledge gained from studying this enzyme, we are identifying other physiologically relevant retinol metabolizing enzymes.

Additionally, in collaboration with Dr. Lonny Levin's laboratory, we have identified a new form of adenylyl cyclase, the enzyme producing the ubiquitous second messenger, cAMP. Currently, we are studying the expression pattern, biochemical regulation and physiological function of this novel, and mammalian soluble adenylyl cyclase.

**RECENT PUBLICATIONS**


**Grün, F., Noy, N., Hämmerling, U., and Buck, J. Purification, cloning and bacterial expression of retinol dehydratase from Spodoptera frugiperda . J. Biol. Chem. 271:16135-16138, 1996.**

**Chen, Y., Derguini, F., and Buck, J. Vitamin A in serum is a survival factor for fibroblast. Proc. Natl. Acad. Sci. USA 94:10205-10208, 1997.**


*Pharmacology*

# Paolo Casali, M.D.

## HUMAN B CELL DIFFERENTIATION AND ANTIBODY GENE SELECTION

Dr. Casali's laboratory combines genetic, biochemical, and cell biology methodologies to analyze the differentiation of human B cells and the maturation of the specific antibody response in response to antigen. Specifically, we want to understand how B lymphocytes undergo a coordinated differentiation program that eventually leads to the generation of class-switched and high affinity antibodies to foreign antigens, mainly those on viruses and bacteria, and self-antigens, such as DNA.

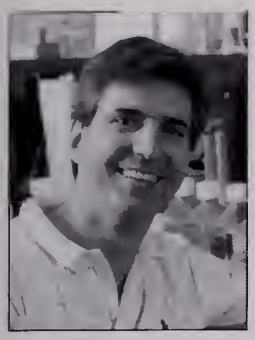
In the antigen-dependent stage of B cell differentiation, which is fostered by the microenvironment of the germinal center (GC) of secondary lymphoid organs, antigen recruits B cells expressing an Ig receptor for antigen (BCR) in unmutated configuration, and drives them through Ig heavy chain class switching and V(D)J gene somatic hypermutation to fine tune and potentiate the specific antibody response (maturation of the antibody response). The understanding of the mechanisms that underlie Ig class switching and somatic hypermutation has been severely limited by the lack of a suitable *in vitro* B cell differentiation model. We have recently identified a unique human monoclonal line (CL-01 cells) that can be induced to recapitulate GC B cell differentiation. These cells are $IgM^+$ $IgD^+$, express the phenotype of GC founder centroblasts, and, in response to physiological stimuli, switch to IgG, IgA, and IgE, and effectively mutate the expressed Ig $V_HDJ_H$ and $V\lambda J\lambda$ genes. Analysis of CL-01 cells has shown that CD40:CD40L engagement is crucial for the induction of Ig class switching. This is part of coordinated differentiation program that modulates the expression of several surface molecules, including CD30, CD38, and CD77, and that eventually leads, in the presence of IL-6, to plasmacytoid differentiation. This differentiation program can be induced to include Ig V(D)J somatic hypermutation upon application of different and discrete stimuli, i.e., BCR engagement and co-engagement of other T:B cell co-stimulatory molecules in addition to CD40. CL-01 cells are presently used to address the requirements, the modalities, and the mechanisms of Ig class switching and somatic hypermutation, including the analysis of signaling pathways emanating from CD40, CD30, and BCR, and their impact on the regulation of the transcription and recombination of the Ig locus. The laboratory's activity extends to the analysis of the dysregulation of the above mechanisms in autoimmunity and B-cell lymphomagenesis to define the relationships between health and disease state.

**RECENT PUBLICATION**


**Cerutti, A., Schaffer, A., Shah, S., Zan, H., Liou, H.-C., Goodwin, R.G., and Casali, P. CD30 is a CD40-inducible molecule that negatively regulates CD40-mediated immunoglobulin class switching in non antigen-selected human B cells. Immunity 9:239-246, 1998.**

**Zan, H., Cerutti, A., Schaffer, A., Dramitinos, P., and Casali, P. CD40 engagement triggers switching to IgA1 and IgA2 in human B cells through induction of endogenous TGF-β. Evidence for TGF-β but not IL-10-dependent direct Sμ→Sα and sequential Sμ→Sγ, Sγ→Sα DNA recombination. Journal of Immunology 161:5217-5225, 1998.**


*Immunology*



# Daniel F. Catanzaro, Ph.D.

## MOLECULAR BIOLOGY OF THE RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system (RAS) plays a key role in the maintenance of normal blood pressure through its effects on vascular tone and electrolyte metabolism. Accordingly, many of the drugs used to treat hypertension are directed at the RAS (angiotensin converting enzyme inhibitors, angiotensin II antagonists, etc). Although recent transgenic models show that hypertension may be produced by altering the expression of normal RAS gene products, derangements of the RAS that cause human hypertension are not known. The aims research conducted in this laboratory are (i) to investigate the molecular mechanisms of RAS gene expression with a view to understading normal RAS function, its role as a target of pharmacologic antihypertensive treatments, and its involvement in the pathogenesis of hypertension; and (ii) to explore novel mechanisms of renin and prorenin uptake by tissues.

***Mechanisms of Cell-Specific Renin Gene Expression:*** Our recent studies have focused on the mechanisms that direct appropriate cell-specific expression of the human renin gene (1). This has led to important developments in human RAS transgenic models. Such models take advantage of the species-specificity of the cleavage of angiotensinogen by renin: human renin will not cleave mouse angiotensinogen, and mouse renin will not cleave human angiotensinogen. Thus, transgenic lines harboring either the human renin (hREN) or human angiotensinogen (hAOGN) genes display no significant blood pressure (BP) phenotype. However, when mated together to yield doubly-transgenic lines expressing both hREN and hAOGN, a functional hRAS is formed. New hREN transgenic lines in which plasma human renin originates from the kidney permit studies of the regulation of synthesis and secretion of renal renin, uptake of renin by vascular tissues.

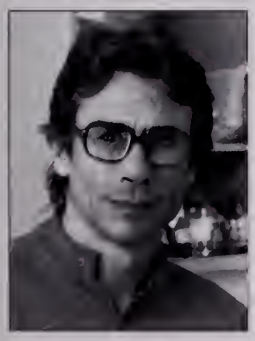
***Characterization and Cloning of a Renin Binding Site:*** The presence of renin in some tissues and its disappearance after the removal of the kidneys suggests that it might be taken up from the circulation. The effects of renin in tissues have been implicated in cardiovascular disease and in the protective effect of drugs that act on the renin system. Recently, we identified a site in membrane preparations of several rat tissues that specifically binds both renin and its precursor, prorenin, with high (2) affinity. Studies in progress seek to determine the region(s) of the renin/prorenin molecule involved in binding in vitro and to clone the binding site. These studies will provide agonists and antagonists that will ultimately enable us to establish the relationship between renin/prorenin binding *in vitro*, and the site(s) that mediate the physiological effects of renin and prorenin in vivo.

**RECENT PUBLICATIONS**


**Yan, Y., Jones, C.A., Sigmund, C.D., Gross, K.W., Catanzaro, D.F. Conserved enhancer elements in human and mouse renin genes have different transcriptional effects in As4.1 cells. Circ Res. 81:588-566, 1997.**

**Sealey, J.E., Catanzaro, D.F., Lavin, T.N., Gahnem, F, Pitarresi, T., Hu, L-F, Laragh ,J.H. Specific prorenin/renin binding (ProBP): identification and characterization of a novel membrane site. Am J Hypertens 9:491-502, 1996.**


*Physiology, Biophysics & Molecular Medicine*



# Michael A. Caudy, Ph.D.

## MOLECULAR GENETIC ANALYSIS OF DROSOPHILA NEUROGENESIS

A central question in biology is how different cells become "determined" to follow different developmental pathways and, therefore, express different sets of genes. The focus of our lab is to understand the molecular-genetic mechanisms which control neuronal cell determination in the fruitfly, *Drosophila*. In flies the peripheral nervous system (PNS) is relatively simple, and it is possible to identify PNS neurons at the single cell level. Genetic analysis of *Drosophila* development has revealed genes which control the determination of specific identified neurons within the PNS. At present, about 17 genes are known which control PNS cell determination in fruit flies.

Of these 17 genes, at least 10 belong to a family of homologous genes coding for DNA-binding proteins called helix-loop-helix (HLH) proteins. These proteins regulate neuronal cell determination by binding to the regulatory domains of genes involved in neuronal cell development, and controlling their transcription. In addition to binding to DNA, the HLH proteins also can bind to each other to form multi-protein complexes which have different DNA-binding properties. Some of the HLH proteins act as activators and some act as repressors of neuronal cell determination. A current focus of our lab is to understand the molecular interactions of these proteins with each other, and with their target DNA. The *Drosophila* HLH genes are of additional interest because HLH genes also are found in humans and other mammals. In humans at least two HLH genes are proto-oncogenes which normally control gene regulation during development, but which produce cancer when mutated or misexpressed.

Areas of graduate training in our lab include developmental neurobiology, molecular biology, genetics, and protein biochemistry.

**RECENT PUBLICATIONS**


**Ohsako, S., Hyer, J., Panganiban, G., Oliver, I. and Caudy, M. Hairy function as a DNA binding HLH repressor of *Drosophila* sensory organ formation. Genes Dev. 8:2743-2755.**

**Fisher, A., Ohsako, S. and Caudy, M. The WRPW motif of Hairy-related bHLH repressor proteins acts as a four amino acid transcription repression and protein-protein interaction domain. Mol. Cell. Biol. 16:2670-7, 1996.**


*Cell Biology & Genetics*

*Neuroscience*

# Ethel Cesarman, M.D., Ph.D.

## HUMAN TRANSFORMING HERPES VIRUSES

Our laboratory is involved in studying the process of viral oncogenesis in human cancer. We are interested in the molecular characterization of immunodeficiency-associated non-Hodgkin's lymphomas, including those associated with AIDS, as well as those presenting in solid organ transplant recipients, many of which are associated with Epstein-Barr virus (EBV) infection. However, much of our recent research is focused on the characterization of the Kaposi's sarcoma-associated herpesvirus (KSHV), also called human herpesvirus 8(HHV8), especially as it relates to cellular transformation and oncogenesis. Our laboratory was involved in the recent identification of this infectious agent which is invariably present in Kaposi's sarcoma, whether presenting in HIV-positive or negative patients. We have also identified its consistent presence in the rare subset of non-Hodgkin's lymphomas called primary effusion (or body cavity-based) lymphomas. These lymphomas have been used by us and others to establish cell lines, which are still the only efficient system to grow and produce KSHV *in vitro*, and represent the most widely used substrate for serologic analysis for assessment of KSHV infection. We have recently achieved infection of primary human endothelial cells with KSHV, resulting in the transformation of these cells, and providing the first direct evidence that KSHV plays a transforming role in the pathogenesis of KS.

Characterization of this virus is a developing area still at its early stages and with many aspects to be explored. This virus contains homologs to more than ten cellular genes involved in cellular proliferation, differentiation, inflammation and/or survival, including IL-6, cyclin D, MIP-like chemokines, a chemokine receptor, BCL-2, FLIP, and IRF. Our ongoing research involves multiple aspects of this virus, including studies such as binding and transmission, analysis of virally encoded proteins, and studies to determine the role of HSV in transformation and development of malignant lymphoma and Kaposi's sarcoma.

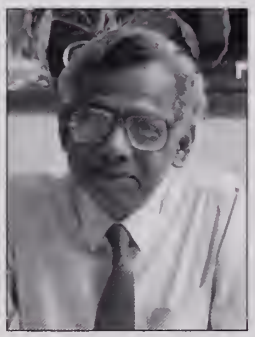
**RECENT PUBLICATIONS**


**Cesarman, E., Chang, Y., Moore, P.S., Said, J.W. and Knowles, D.M. Kaposi's sarcoma-associated herpesvirus-like DNA sequences are present in AIDS-related body cavity based lymphomas. New Engl. J. Med. 332:1186-1191, 1995.**

**Arvanitakis, L., Geras-Raaka, E., Gershengorn, M.C. and Cesarman, E. KS herpesvirus encodes a constitutively active G protein-coupled receptor linked to cell proliferation. Nature 385:347-350, 1997.**


*Cell Biology & Genetics*

*Immunology*



# Raju S.K. Chaganti, Ph.D.

## HUMAN CANCER GENETICS

The aims of this laboratory are to study, using cytogenetic and molecular genetic methods, the role played by hereditary factors in the origin of human cancer and the relationship between malignant transformation and expression of differentiated phenotypes in tumor cells. Two tumor types are under intensive study. One is non-Hodgkin's lymphoma that arises in lymphoid cells during their lineage (B- and T-) differentiation. In these tumors, a number of protooncogenes are deregulated as a result of chromosome translocations, which bring them in juxtaposition with the immunoglobulin and T-cell receptor genes. Studies are directed towards analysis of the role of deregulated expression of known protooncogenes in the development of phenotypes expressed by the tumors and tumor cells, and isolation and characterization of novel genes that undergo deregulation as a result of transposition. The other tumor type under study is the germ cell tumor in males. These tumors arise in premeiotic germ cells whose normal development program dictates cessation of proliferation as they complete the premeiotic S phase and terminal differentiation into gametes. Proliferation and (embryonal) differentiation, normally postponed until after fertilization, are abnormally elicited in transformed premeiotic cells. Studies are directed towards isolating the gene(s) responsible for the transformation and molecular basis for the embryonal-like differentiation of these tumors. A unique aspect of this laboratory's approach is relating the findings at the basic level to the clinical realm. Thus, the utility of specific genetic changes in tumors discovered in the research laboratory to diagnostic and prognostic evaluation of patients is investigated and, when appropriate, applied to patient management in collaboration with the clinical staff. Human tumor and normal cells are the materials for study utilizing a wide variety of methods, such as cell culture, chromosome analysis, and structure-function analysis of genes making use of modern molecular biological techniques.

**RECENT PUBLICATIONS**


**Dyomin, V.G., Rao, P.H., Dalla-Favera, R., and Chaganti, R.S.K. BCL8, a novel gene involved in translocations affecting band 15q11-13 in diffuse large cell lymphoma. Proc. Natl. Acad. Sci. USA 94:5728-5732, 1997.**

**Houldsworth, J., Reuter, V., Bosl, J.G., and Chaganti, R.S.K. Aberrant expression of cyclin D2 is an early event in human male germ cell tumorigenesis. Cell Growth and Differentiation 8: 239-299, 1997.**


*Cell Biology & Genetics*

# Walter W. Y. Chan, Ph.D.

## PHARMACOLOGY OF OXYTOCIN AND VASOPRESSIN PEPTIDES

Oxytocin (OT) and vasopressin (VP) were first discovered as hormones of the posterior pituitary gland. It is now known that these two peptide hormones are also found in the CNS as neurotransmitters and in numerous organs having important autocrine and/or paracrine functions. OT and VP have multiple biological functions involving the kidney, the cardiovascular, the reproductive systems, and cognitive and behavioral effects. Four receptor subtypes, $V_{1a}$, $V_{1b}$, $V_2$ and OT, have been identified. The diverse multiple biological actions of OT and VP suggest the existence of additional and yet to be identified new receptor subtypes.

The focus of our research is on determining the structure-activity-relationship of OT/VP peptides, with the aim of designing and synthesizing selective agonists or antagonists that would have value as research probes for elucidating the various physiological functions of OT and VP and their receptors and as therapeutics for the treatment of diseases caused by dysfunctions of OT and VP. Our current efforts are on the development of selective OT-antagonists, $V_2$-receptor antagonists and novel hypotensive VP peptides.

OT-antagonists are tocolytic agents and have potential therapeutic value in the prevention of premature birth. Preterm birth is a major cause of neonatal mortality and morbidity. Effective therapy for preterm birth has not been developed. Successful prevention of premature birth would have the single greatest impact on reducing infant mortality.

V2-receptor antagonists and hypotensive VP peptides under development in our laboratories could lead to the introduction of novel aquretic agents (new diuretics) and a new class of antihypertensive drugs for the treatment of cardiovascular and hypertensive diseases.

**RECENT PUBLICATIONS**


Chan, W.Y., Wo, N.C., and Manning, M. The role of oxytocin receptors and vasopressin $V_{1a}$ receptors in uterine contractions in rats: Implication for tocolytic therapy with oxytocin antagonists. AM. J. Obstet. Gynecol. 175:1331-1335, 1996.

Chan, W.Y., Wo, N.C., Stoev, S., Cheng, L.L., and Manning, M. Discovery of novel selective hypotensive vasopressin peptides: A new vasodilating vasopressin receptor? In: Vasopressin and Oxytocin: Synopsis of Recent Advances in Molecular, Cellular and Clinical Research. Zingg, H.H. , Bichet, D.C., and Bourque, C. eds. Plenum Press, New York (in press), 1998.


*Pharmacology*

# Selina Chen-Kiang, Ph.D.

## CYTOKINE SIGNALING AND B-CELL DIFFERENTIATION

A central question in biology and medicine is how cellular differentiation is coupled to cell cycle control and cell death. Terminal differentiation of B cells to plasma cells, which is essential for the humoral immune response, represents one of the most prominent examples. Dysregulation of B-cell terminal differentiation is the cause of major lymphoid cancers, as B-cell lymphomas arise from the failure of B-cells to undergo terminal differentiation and multiple myelomas result from the uncontrolled accumulation of plasma cells.

We have developed two *in vitro* systems to study B-cell activation and terminal differentiation. In one, stimulation of human B-cells activated by the Epstein-Barr Virus with the cytokine IL-6 leads to simultaneous reversal of EBV immortalization and activation of the terminal differentiation program. This study has revealed for the first time the cyclin-dependent kinase inhibitors and caspases that are crucial for differentiation-coupled cell cycle arrest and apoptosis during B cell terminal differentiation. Work is in progress to elucidate the mechanism by which IL-6 represses EBV immortalization and to control EBV immortalization by cytokines. We have further reconstituted B-cell activation and terminal differentiation in primary mouse B-cells *in vitro*. This makes it possible to determine the cytokines, cell cycle regulator and caspases that are essential for B-cell activation and terminal differentiation in primary B-cells. In conjunction with transgenic and knockout mice, we have begun to elucidate the contributions of cytokine-signaled cell cycle control and cell death to normal B-cell terminal differentiation and tumorigenesis. B-cell terminal differentiation is associated with bone-remodeling. To understand this process better, we are further investigating cytokine signaling and osteogenesis in primary marrow stromal and bone-derived cells.

**RECENT PUBLICATIONS**


Zhang, X., Blenis, J., Li, H-C., Schindler, C., and Chen-Kiang, S. Requirement of serine phosphorylation for formation of STAT-promoter complexes. Science 267: 1990-1994, 1995.

Morse, L.M., Chen, D., Franklin, D., Xiong, Y. and Chen-Kiang, S. Induction of cell cycle arrest and B cell terminal differentiation by CDK inhibitor P18ink4c and IL-6. Immunity 6: 47-56, 1997.


*Immunology*

# Ting-Chao Chou, Ph.D.

## BIOCHEMICAL PHARMACOLOGY

Dr. Chou's major research objectives are the study of: (1) the mechanisms of action of antitumor DNA cleaving, multi-drug resistance (MDR) reversing, and tubulin-targeting agents; (2) the biochemical and pharmacological bases for the selectivity of effects on different targets; (3) preclinical evaluation of new compounds *in vitro* and *in vivo* for cancer therapeutic potential; and (4) the derivation of theoretical formulations for dose-effect relationships that i) permits the automated computer analysis of relative potency and therapeutic index, and ii) facilitates the study of the interaction of multiple drugs in combination chemotherapy. The compounds of current interest include: Enediynes that directly cleave DNA, and chempothecin, rebecamycin, straurosporin derivatives and acridine carbamate that exerts DNA topoisomerase type I or type II mediated DNA cleavage. We also studied the pharmacological consequences of drug interaction with P-glycoprotein or multidrug resistance related protein, MDR reversal, collateral sensitivity and synergistic effects. The reverse prenyl compounds such as ardeemins, that sensitize MDR cells to antitumor agents have been studied in terms of MDR-reversal and synergistic effects. Emphasized are pharmacodynamics, the determination of affinity and efficacy of drug interaction with membrane proteins or microtubule, and the elucidation of molecular events following the binding or incorporation of a drug into macromolecules. Recent thrust includes the development of a new class of 16-member macrolides (e.g., epothilones) that stabilize microtubule assemblies.

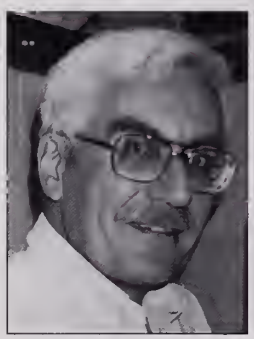
One of the major developments in the past years in this laboratory has been the introduction of a new quantitative method for analyzing the combined effects of chemotherapeutic agents. This method takes into account the "shape" of dose-effect curves and the relative "potency" of each drug and their mixture in terms of determined parameters. The median-effect equation of Chou (1976) and the combination index (CI) equation of Chou-Talalay (1981) have been used in scientific papers published in over 190 biomedical journals. The method has been widely used to analyze: (1) quantitation of combined drug effect interactions of various anticancer agents: (2) synergistic combinations of anti-HIV agents and (3) the combination of immunosuppressants for organ transplantation. Computer software programs for automated analysis with IBM PC have been developed.

**RECENT PUBLICATIONS**


**Aghl, M., Kramm, C.M., Chou, T.-C., Breakefield, X.O., and Chiocca, A. Synergistic anticancer effects of the ganciclovir/thymidine kinase and 5-fluorocytosine/cytidine deaminase gene therapies. J. Nat. Cancer Inst. 90:370-380, 1998.**

**Chou, T.-C., Depew, K.M., Zheng, Y.-H., Safer, M.L., Chan, D., Helfrich, B., Zatorska, D., A. Bornmann, W., and Danishefsky, S.J. Reversal of anticancer multidrug resistance by the ardeemins. Proc. Natl. Acad. Sci. USA. (in press) 1998.**


*Pharmacology*



# Arthur J. L. Cooper, Ph.D.

Areas of interest:

α-keto acid chemistry and biochemistry; pyridoxal 5'-phosphate enzymes; design of enzyme inhibitors as drugs; amino acid and ammonia metabolism in normal and disease states: cerebral energy metabolism (with emphasis on the malate aspartate shuttle) and its disruption in various disease states; neurochemical consequences of cerebral ischemia; molecular biology of glutamine transaminase K/cysteine S-conjugate-b-lyase and w-amidase.

Neurochemical Studies.

1. In liver disease brain function is compromised. Disruption of nitrogen metabolism results in excessive ammonia levels and associated brain impairment. One theory suggests that ammonia is toxic to the CNS by inhibiting the malate aspartate shuttle (MAS) (necessary for the transport of reducing equivalents from cytosol to mitochondrion). We have designed new "suicide" inhibitors of aspartate aminotransferase, a key component of the shuttle. Such inhibitors have provided insights into the mechanism of the MAS in neural tissues.

2. Cerebral tissue is susceptible to ischemic damage. The damage results from the interplay of a number of factors (e.g., low pH, free radical formation, glutamate hyperexcitation). We have designed new inhibitors of lactate dehydrogenase. These will be tested as a means of lowering lactate levels following an ischemic insult to neural tissues.

3. Some organic solvents, including halogenated hydrocarbons are neurotoxic to humans. An example is trichloroethylene, which via its breakdown produed to dichlorovinyl cysteine (DCVC). This compound is bioactivated by glutamine transaminase K/cysteine S-conjugate b-lyase, an enzyme first discovered by Cooper and Meister. We have cloned and sequenced the kidney cytosolic enzyme. We are attempting to understand the mechanism of the neurotoxicity to humans. We have also recently discovered a new lyase in the kidney and are in the process of characterizing it.

4. Mice with an inherited form of type-II diabetes exhibit altered brain metabolism. We have shown that the capacity for cerebral fatty acid oxidation is greatly increased and the fatty acids content is greatly diminished in these animals. We have also shown that the cerebral antioxidant defense mechanisms of these animals are altered. Glutathione (a major defense against oxidative stress) was shown to be more prevalent in cultured astrocytes than in neurons.

**RECENT PUBLICATIONS**


**Abraham DG, Patel P, and Cooper AJL Characterization of a high molecular weight cysteine-S-conjugate b-lyase from rat kidney with activity toward leukotriene E4. J. Biol. Chem. 270, 180-188, 1995.**

**Makar TK, Hungund BL, Cook GA, Kashfi K, and Cooper AJL. Lipid metabolism and membrane composition are altered in the brains of type II diabetic mice. J. Neurochem. 64, 2159-2168, 1995.**


*Neuroscience*

# Mary K. Crow, M.D.

## THE ROLE OF T-B LYMPHOCYTE INTERACTIONS IN THE INDUCTION OF NORMAL IMMUNE RESPONSES AND IN THE PATHOGENESIS OF AUTOIMMUNE DISEASES

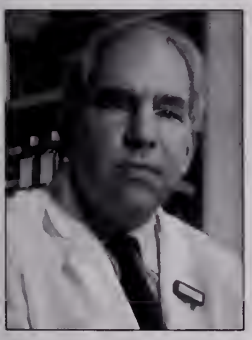
T-cell help for B-cell activation and differentiation is central to the regulation of normal immune responses and is a requirement for induction of pathogenic autoantibody production and systemic autoimmunity. Dr. Crow's laboratory is investigating the role of interactions among these immune system cells, as well as soluble lymphocyte products, in the pathogenesis of SLE. Of particular interest is the Th cell surface molecule CD40 ligand (CD40L), which is briefly expressed on the T-cell following activation through the T-cell antigen receptor, and which mediates B-cell activation, immunoglobulin class switch to mature isotypes, and the induction of cytokine secretion and adhesion molecule expression on macrophages and endothelial cells. The regulation of CD40L expression on Th cells from patients with SLE is an active area of investigation. Dr. Crow's laboratory has shown that CD40L is constitutively expressed on the T cells from some patients with active SLE, and the cell surface expression of CD40L is prolonged following T cell activation. In addition, elevated levels of a soluble form of the CD40L molecule have been documented in the sera of patients with SLE, and the molecular and functional properties of the soluble form of the molecule are being characterized. Excessive expression of CD40L in SLE may promote cell-cell interaction and target cell activation, resulting in IgG secretion, as well as vascular damage, perhaps contributing to arterial thrombosis or vasculopathy. Given the essential role of the CD40L-CD40 pathway in autoantibody secretion, as well as endothelial cell activation, interruption of this pathway may play a profound role in reducing autoimmunity and tissue damage in SLE. In addition to lymphocyte cell surface molecules, soluble cytokines can contribute to immune system regulation. Dr Crow's laboratory has been studying the role of the multifunctional cytokine, interleukin-10 (IL-10) in the impaired T-cell function that is characteristic of patients with SLE. It was observed that SLE T cells are activated *in vivo*, and that a proportion of those cells undergo programmed cell death through the FasL-Fas receptor pathway when cultured in vitro. IL-10 produced in high concentrations by patients with clinically active SLE promotes T-cell apoptosis, and neutralizing anti-IL-10 antibody rescues SLE T cells from cell death. Activation-induced cell death of SLE T cells, augmented by IL-10, may result in impaired cellular immunity and increased susceptibility to infection. In addition, the apoptotic cells may be an important source of autoantigens *in vivo*. These experiments suggest that manipulation of IL-10 levels *in vivo* may have therapeutic utility in systemic autoimmunity and other syndromes characterized by chronic and ongoing T-cell activation.

**RECENT PUBLICATIONS**


**Koshy, M., Berger, D., Crow, M.K. Increased expression of CD40 ligand on systemic lupus erythematosus lymphocytes. J Clin Invest 98: 826-837, 1996.**

**Georgescu, L., Vakkalanka, R.K., Elkon, K.B., Crow, M.K. Interleukin-10 promotes activation- induced cell death of SLE lymphocytes mediated by Fas ligand. J Clin Invest, 100: 2622-2633, 1997.**


*Immunology*



# Ronald G. Crystal, M.D.

## GENE THERAPY

Our major research interests are in *in vivo* gene transfer, a new technique for transferring genes and appropriate controlling elements to specific organs. This technique has important consequences for both research and patient care, as it permits analysis of gene expression in the relevant physiologic milieu and also the treatment of hereditary and acquired diseases. The laboratory, which forms the major research arm of the Division of Pulmonary and Critical Care Medicine, is new to the Cornell medical campus, having just moved from the National Heart, Lung and Blood Institute of the National Institutes of Health.

The hurdle for *in vivo* gene transfer is to transfer efficiently a site in the target cell where it can effectively express the gene of interest. The laboratory has focused on a number of vector systems, including retrovirus, liposome, and adenovirus. The best vector to accomplish this task is, by far, replication-deficient recombinant adenovirus. With such vectors, it is possible to transfer efficiently genes to the lung, liver, vasculature, heart, skin, muscle and CNS, with high-level expression for weeks to months, depending on the organ. Capitalizing on this system, it became feasible to transfer the human cystic fibrosis transmembrane conductance regulator (CFTR) gene (the normal gene that is the site of mutations that cause cystic fibrosis) to the airway epithelium in experimental animals *in vivo*. This observation forms the basis for an ongoing human trial of gene therapy for the respiratory manifestations of cystic fibrosis.

*In vivo* gene transfer technology has opened a broad range of therapeutic possibilities for the treatment of hereditary and acquired disease, in which the gene is the drug. In this regard, instead of using genes to produce proteins *in vivo*, which then have to be purified before administration to the patient, *in vivo* gene therapy uses the patient as the "factory" to produce the therapeutic protein. In addition to therapeutic uses, the ability to transfer genetic information *in vivo* has brought a new era of experimentation in physiology, as it is now possible to evaluate the responses of specific genetic material to the myriad of known and unknown signals in the intact organism.

**RECENT PUBLICATIONS**


**Mastrangeli A, Harvey B-G, Yao J, Wolff G, Kovesdi I, Crystal RG, Falck-Pedersen E. "Sero-switch" adenovirus-mediated in vivo gene transfer: Circumvention of anti-adenovirus humoral immune defenses against repeat adenovirus vector administration by changing the adenovirus serotype. Hum Gene Ther 7:79-87, 1996.**

**Wolff G, Mastrangeli A, Heinflink M, Falck-Pedersen E, Gershengorn MC, Crystal RG. In vivo adenovirus-mediated ectopic expression of receptors to modulate organ function: Regulation of blood glucose by thyrotropin releasing hormone following ectopic expression of thyrotropin releasing hormone receptors. Nature Genet 12:274-279, 1996.**


*Physiology, Biophysics & Molecular Medicine*

# Lisa R. Denzin, Ph.D.

## ANTIGEN PROCESSING

Class II major histocompatibility molecules (MHC) bind exogenously derived antigenic peptides and present them to CD4+ T cells. The primary focus of our lab is to understand the biosynthetic pathway that results in peptide-loaded MHC class II molecules.

### The Class II Antigen Processing Pathway

MHC class II molecules are cell surface expressed heterodimeric glycoproteins ($\alpha\beta$) that assemble in the ER with a third transmembrane glycoprotein, the invariant chain (I chain). Once fully assembled, the complex moves through the Golgi apparatus and is sorted by a signal in the cytoplasmic domain of the I chain into late endosome-like compartments called MIIC (for MHC class II Compartment). Once in the MIIC, the I chain is proteolytically cleaved from the class II molecules by aspartic and cysteine proteases until only a small fragment of the I chain (CLIP for CLass II-associated Invariant chain Peptides) remains bound in the peptide binding cleft of the class II molecule. The class II-bound CLIP peptide, which functions to protect the class II binding groove until an antigenic peptide can be bound, is then released by the action of another class II-like molecule, HLA-DM. The released $\alpha\beta$ dimers are loaded by HLA-DM with peptides derived from internalized pathogen or endogenous proteins present in the endocytic system and transported to the cell surface.

### The Mechanism of HLA-DM Function

Peptide loading of class II molecules is catalyzed by the action of DM. However, this is not the only function of DM. Recent results showed that DM also functions as a specialized chaperone by stabilizing "empty" or peptide-free class II molecules. Furthermore, DM functions as a peptide editor, ensuring that only appropriate peptides are presented on the cell surface. The mechanism by which DM mediates these various function is completely unknown and therefore, a major goal of our lab is to determine how DM exerts its many functions.

**RECENT PUBLICATIONS**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**Denzin, L.K., D.B. Sant'Angelo, C. Hammond, M.J. Surman and P. Cresswell. Negative Regulation by HLA-DO of MHC Class II-Restricted Antigen Processing. Science 278:106-109, 1997.**


*Immunology*

# Tamara Doering, M.D., Ph.D.

## BIOCHEMISTRY & CELL BIOLOGY OF FUNGI

Glycosyl phosphatidylinositol (GPI) anchors are glycolipid structures which are added to the C-termini of diverse eukaryotic proteins. While the main function of these glycolipids is to tether proteins to cell surfaces, they have also been implicated in targeting and surface mobility of polypeptides, attachment of fungal proteins to the cell wall, signal transduction, and human disease. One of my interests is the role of GPIs in intracellular protein traffic.

Intracellular traffic, or movement of polypeptides between membrane-bound compartments, occurs *via* vesicular transport and is fundamental to numerous cellular processes. Acquisition of GPI anchors is required for the exit of certain proteins from the endoplasmic reticulum (ER) in the yeast *Saccharomyces cerevisiae*. This leads to questions of which protein or lipid factors interact with GPIs to mediate this requirement. We are investigating these issues using techniques such as polypeptide crosslinking, reconstituted *in vitro* transport of engineered proteins, *in vivo* characterization of lipid synthesis mutants, and genetic screens. The ability to use biochemistry and genetics makes *S. cerevisiae* an excellent experimental system, which is also being used to examine yeast-specific features of GPI biosynthesis.

An exciting new area of investigation is the biology of *Cryptococcus neoformans*. This pathogenic fungus is responsible for infections in the growing numbers of patients who are immunocompromised due to HIV, malignancy, or treatment protocols. We are interested in unique aspects of cryptococcal biology which are of biochemical interest and will also suggest possible targets for badly needed antifungal chemotherapy.

One ongoing *C. neoformans* project is to study biosynthesis of the fungal polysaccharide coat, a unique structure which is required for virulence and is thus an attractive drug target. Another is to investigate unique aspects of GPI biosynthesis in this organism. Current techniques include *in vitro* glycolipid biosynthesis, lipid and carbohydrate analysis, and protein purification.

**RECENT PUBLICATIONS**


**Doering, T. L. and Schekman, R. GPI-anchor attachment is required for Gas1p transport from the endoplasmic reticulum in COP II vesicles. EMBO J. 15:182-191, 1996.**

**Doering, T. L. and Schekman, R. GPI anchor attachment in a yeast in vitro system. Biochem. J. 328:669-675, 1997.**


*Pharmacology*

# Dale Dorsett, Ph.D.

## GENE EXPRESSION AND TRANSPOSABLE ELEMENTS

In higher eukaryotes, many genes are developmentally regulated by multiple tissue-specific transcription enhancers. Enhancers are unique because they can regulate promoters several kilobases away. Not all eukaryotes have enhancers. The Upstream Activating Sequences (UASs) of the yeast *Saccharomyces cerevisiae*, similar to enhancers in many other ways, only function when within a kilobase or so upstream of the promoter. However, in yeast, enhancers behave like UAS elements. Therefore, the ability to activate transcription from several kilobases away is not an intrinsic property of enhancer-binding proteins. We posit that higher eukaryotes have additional factors that structurally facilitate long distance enhancer-promoter interactions.

The *suppressor of Hairy-wing* protein (Suhw) of *Drosophila melanogaster* interferes with enhancer-promoter interactions when bound to a transposable element insertion between an enhancer and promoter. However, enhancers promoter-proximal to the bound Suhw still activate the promoter, and an enhancer blocked by Suhw can still activate a second promoter located on the other side. Therefore, Suhw does not affect the activity of enhancer-binding proteins, but somehow interferes with enhancer-promoter communication.

We are looking for the genes that regulate a remote wing margin-specific enhancer in the Drosophila *cut* gene. Some may encode the factors targeted by Suhw that facilitate enhancer-promoter communication. Two known genes, *scalloped* and *mastermind*, and two novel genes, *Chip* and *Nipped*, have been identified. The Scalloped protein binds the wing margin enhancer, and genetic evidence suggests that Mastermind protein also interacts with the enhancer. In contrast, *Chip* mutations hypersensitize the enhancer to Suhw blocking activity. Chip is a widely-expressed chromosomal protein required for activity of several enhancers beginning early in development. Chip interacts directly with several homeodomain transcription factors, and we are studying the mechanisms by which Chip and homeodomain proteins support enhancer-promoter interactions.

**RECENT PUBLICATIONS**


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*Molecular Biology*

# Daniel N. S. Duch, Ph.D.

## ANESTHETIC ACTIONS ON VOLTAGE-GATED IONIC CHANNELS

The cellular and molecular interactions by which anesthetic agents cause the clinical state of "anesthesia" are currently unknown at every level of examination, from the whole organism down to specific molecular interactions. Part of the reason for this lack of understanding is that anesthetics are hydrophobic drugs which dissolve into virtually all cellular and subcellular membranes during anesthesia, thus obfuscating the identification of specific cellular and molecular targets. Nonetheless, these targets are generally believed to be the ligand- and voltage-gated ionic channels which underlie cellular excitability and intercellular communication. Most theories of anesthetic action can be divided into two categories: 1) Anesthetics alter ionic channel function directly by binding to the channel protein itself; or 2) Anesthetics alter channel function indirectly by altering the physicochemical properties of the membrane lipids which surround the channel. Implicit in the latter mechanism is the assumption that membrane protein function depends, at least in part, on the properties of the surrounding lipids.

Our laboratory is investigating the interactions of anesthetics with single voltage-gated ionic channels, examining and defining the archetypal anesthetic interactions which may account for the myriad of clinically observed manifestations of anesthesia. To help understand the role that membrane lipids play in the anesthetic response, we have been incorporating purified and unpurified voltage-gated sodium channels from several sources, including human brain and electric eel, into artificial planar bilayer membranes for electrophysiological recording of their interactions with various classes of anesthetics. Planar lipid bilayer methodology allows the lipid composition of the membrane in which the channel is placed to be controlled to a greater extent than with almost any other technique presently available. These experiments will probe the role of the lipid milieu in the anesthetic response, as well as examine the role that membrane lipids play in defining or altering ionic channel function.

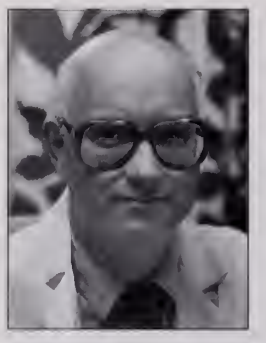
More recently, we have begun to examine the interactions of anesthetics with sodium channels from rat muscle and brain expressed in stably transfected Chinese Hamster Ovary cell lines using whole cell patch clamp techniques. These experiments will help to determine the role that differences in protein structure play in mediating the anesthetic response.

**RECENT PUBLICATIONS**


**Rehberg, B., Xiao, Y.-H. and Duch, D.S. Central nervous system sodium channels are significantly suppressed at clinical concentrations of volatile anesthetics. Anesthesiology 84:1223-1233, 1996.**

**Frenkel, C., Wartenberg, H. C., Duch, D. S. and Urban, B. W. Steady-state properties of sodium channels from healthy and tumorous human brain. Mol. Brain Res. 59: 22-34, 1998.**


*Physiology, Biophysics & Molecular Medicine*



# Bo Dupont, M.D., D.Sc.

## RECEPTOR-MEDIATED SIGNALS IN T CELLS AND NK CELLS

The overall objectives of this laboratory are to gain insights on signal transduction events which occur when human T lymphocytes and Natural Killer (NK) cells are activated. Our studies are aimed at investigating the signal transduction pathways which are activated following receptor-ligand interactions involving antigen-specific activation (i.e. TCR mediated signals) of T cells and the role played by costimulatory receptors such as CD28, CD2, CD5, and CD7.

The studies are divided into investigations of early activation signals which control the initiation of the signal transduction pathways as well as late events such as the production of the cytokines interleukin-2 (IL-2), interleukin-4 (IL-4), interferon gamma (IFN), and other mediators of immune function. Additional studies concern the investigation of signal transduction events resulting in cytolytic effector functions in T cells and NK cells. The biochemical pathways initiated by receptor-mediated activation of protein tyrosine kinases, protein tyrosine phosphatases and phosphatidylinositol-3-kinase and their differentiated effects on granule exocytosis and cytokine production are currently under investigation. These studies are primarily performed on NK cells. Our main interest at present focuses on the function of the different families of NK receptors that interact with HLA class I molecules. The genetics of NK receptors and the generation of NK receptor repertoire is investigated as well as the signaling pathways initiated by these receptor-ligand interactions.

**RECENT PUBLICATIONS**


King, P.D., Sadra, A., Teng, J.M.C., Liu, X-R., Han, A., Selvakumar, A., August, A., and Dupont, B. Analysis of CD28 cytoplasmic tail tyrosine residues as regulators and substrates for the protein tyrosine kinases, EMT and LCK. Journal of Immunology 158:589-590, 1997.

August, A., Sadra, A., Dupont, B., and Hanafusa, H. Src-induced activation of Inducible T cell kinase (ITK) requires phosphatidylinositol 3-kinase activity and the Pleckstrin homology domain of inducible T cell kinase. Proc. Nat. Acad. Sci. USA 94:11227-11232, 1997.


*Immunology*

# Robert Duvoisin, Ph.D.

## MOLECULAR BIOLOGY OF VISION

The objectives of my laboratory are to use molecular biology approaches to study the normal function of the eye, identify the molecular basis of eye diseases and design possible genetic therapies. Ongoing projects in the laboratory include:

1. Diversity and function of metabotropic glutamate receptors. Glutamate is the major excitatory neurotransmitter in the vertebrate central nervous system. In addition to its role in normal brain processes, such as learning and memory, imbalances in glutamatergic function can result in excitotoxic neuronal cell death or epileptic seizures. To date, eight metabotropic glutamate receptors (mGluRs), i.e. receptors that activate second messenger pathways upon glutamate stimulation, have been identified. *In situ* hybridization and immunohistochemical studies are being done to analyze the pattern of expression of these receptors in normal adult retina and during development and retinal degeneration. The coupling between mGluRs and G proteins and the targeting of mGluRs to pre- and post-synaptic membranes is studied by site-directed mutagenesis. A transgenic mouse in which mGluR8 is "knocked-out" has been generated and will help in unraveling the function of this receptor in the retina and the brain.

2. Mechanism of organelle degradation in the eye lens. The organelles and nucleus of lens fiber cells are degraded during differentiation. Very little is known about this important process necessary for lens transparency. We are investigating the role of lipoxygenase, an enzyme that we have shown serves a similar purpose during red blood cell differentiation, in the lens.

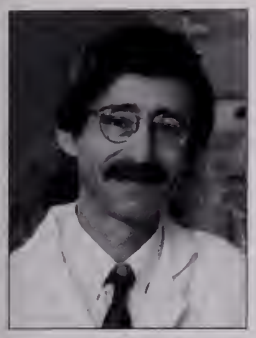
3. Inhibition of retinal neovascularization by Angiostatin. By destroying the organization of retinal cells, neovascularization in the eye is a major source of vision impairment in diabetic retinopathy and in macular degeneration. We are testing the use of recombinant Angiostatin in preventing neovascularization.

**RECENT PUBLICATIONS**


Duvoisin, R.M., Zhang, C. and Ramonell, K. A novel metabotropic glutamate receptor expressed in the retina and olfactory bulb. J. Neurosci. 15: 3075-3083, 1995.

Francesconi, A. and Duvoisin, R.M. Role of the second and third intracellular loops of metabotropic glutamate receptors in mediating dual signal transduction activation. J. Biol. Chem. 273: 5615-5624, 1998.


*Neuroscience*



# Keith Elkon, M.D.

## THE ROLE OF APOPTOSIS GENES IN TOLERANCE AND AUTOIMMUNITY

Fas (APO-1, CD95) is a member of the TNF-R, NGF-R superfamily that triggers programmed cell death (apoptosis). Fas is expressed on activated lymphocytes in the peripheral immune system resulting in the removal of potentially autoreactive lymphocytes. Mutations of the Fas receptor or ligand lead to systemic autoimmunity in mice. We have recently identified humans with Fas mutations that have systemic autoimmunity and lymph node enlargement. The majority of patients have heterozygous mutations that lead to loss of function by a dominant negative effect. Since many of these mutations affect the death domain of Fas, they impair FADD binding and subsequent induction of the caspase cascade required for apoptosis.

Other studies related to apoptosis have focused upon factors that modulate susceptibility to Fas mediated apoptosis of B cells, macrophages, and dendritic cells. Since B cells derived from lupus-like diseases show some impairment in apoptosis, investigation of the signal transduction pathways are in progress. Loss of tolerance leads to autoantibody production in systemic autoimmune disorders. To date, there is no satisfactory explanation for selection of autoantibodies to intracellular nucleoprotein particles such as nucleosomes. We have recently shown that at least some autoantibodies may be targeted against the products of cells undergoing apoptosis. Whereas at least 6 Ced genes in the nematode, C. elegans, encode proteins that are required for engulfment of apoptotic cells, the mechanisms whereby apoptotic cells are efficiently identified, removed, and degraded by phagocytes in mammalian cells are not well understood. We have recently identified novel pathways responsible for the removal of apoptotic cells. The receptors, ligands and effects of perturbation of these receptors on immune function is currently being explored.

**RECENT PUBLICATIONS**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**Orlinick, J.R., Elkon, K.B., Chao, M.V. Separate domains of the human Fas ligand dictate self-association and receptor binding. J. Biol. Chem. 272:32221-32229, 1997.**


*Immunology*

# Nathan A. Ellis, Ph.D.

## CANCER SUSCEPTIBILITY AND GENOMIC INSTABILITY

We are interested in the genetic and molecular analysis of factors that maintain the faithful transmission of the genetic material from cell generation to cell generation. Defects in genes that contribute to this process often result in genomic instability, and one of the major clinical consequences of genomic instability is susceptibility to cancer. As an approach to this problem, we study the rare autosomal recessive entity Bloom's syndrome (BS). Of the various clinical characteristics present in BS, small stature and cancer predisposition are predominant. BS cells are hypermutable as evidenced at the chromosomal level by chromosome breakage and at the level of specific loci by the accumulation of mutations in genes. The most pronounced effect of the BS mutation is a strikingly increased frequency of recombination between homologous chromosomes and between sister chromatids. The BS gene, BLM, encodes a 1417 amino acid protein homologous to the RecQ family of DNA helicases. The function of the RecQ helicases in DNA transactions is not known; however, genomic instability is a feature common to most, if not all, mutations characterized in RecQ helicases so far. Through various molecular techniques (e.g., cell transfection, Western blot, immunoprecipitation, immunofluorescence) we are addressing the question in what aspect of DNA processing does BLM operate? We have identified proteins that interact with BLM and are studying how they act together to maintain genomic stability.

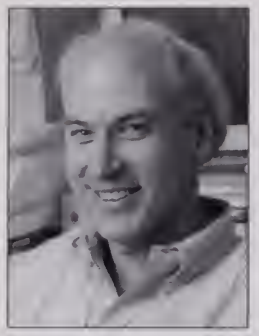
The laboratory also investigates the human molecular genetics of susceptibility to colorectal cancer. A large family study is underway at Memorial Sloan-Kettering – the objective of which is to identify new colon cancer genes. This study in conjunction with the application of new genetic technologies (e.g. high through-put genotyping and microarray analyses) should provide many important insights into the pathogenesis of colorectal cancer.

**RECENT PUBLICATIONS**


**Ellis, N.A., Groden, J., Ye, T., Straughen, J., Lennon, D.J., Ciocci, S., Proytcheva, M., German, J. The Bloom's syndrome gene product is homologous to RecQ helicases. Cell 83:655-666, 1995.**

**Ellis, N.A. DNA helicases in human inherited disorders. Curr. Op. Genet. Devel. 7:354-363, 1997.**


*Cell Biology & Genetics*



# Erik Falck-Pedersen, Ph.D.

## THE BIOLOGY OF ADENOVIRUS GENE TRANSFER VECTORS: BIOCHEMISTRY OF MRNA 3' PROCESSING AND TRANSCRIPTION TERMINATION

Adenovirus vectors play a large role in the two areas of ongoing research in our laboratory. The gene transfer or gene therapy project uses adenovirus vectors to transfer genetic information to a target tissue predominantly in rodent animal models. The RNA processing project uses adenoviral vectors as a tool to dissect out the elements of RNA processing that regulate the maturation of a precursor RNA into a mature mRNA.

The current focus of the gene transfer project can be divided into two sections:

1) To extend our understanding of the adenovirus entry pathway to the nucleus of the target cell study of this area of adenovirus biology will lead to our ability to engineer viruses in a manner that will show us how to manipulate the receptor and uptake pathway used to enter a designated target cell. 2) Subsequent to virus entry, the activation of an immune cascade which is involved targeting cells infected by the viral vectors for elimination by the host immune system as well as induction of a humoral immune response is a second area of current investigation. Once again, the capsid proteins which are involved in the entry and uptake pathway are critical activators of the host immune response to adenovirus infection. Using genetic engineering we are manipulating the capsid proteins to diminish recognition by the host immune system.

The focus of the RNA processing/transcription termination project is directed at understanding the biochemistry of the 3' polyadenylation cleavage event and how this event converts an RNA pol II elongation complex into a termination competent complex. We are using two strategies to accomplish this objective.

1) Using partially purified factors *in vitro*, we are attempting to produce a bona fide processing coupled termination event in a manner which will allow biochemical definition and characterization of the processing signal that generates production of the termination competent pol II complex.

2) Using recombinant adenovirus vectors, we are defining the sequence elements which are responsible for the RNA pol 1 termination, and the context of their function *in vivo*.

**RECENT PUBLICATIONS**


**Prescott, J.C., Liu, L., and Falck-Pedersen, E. Sequence-mediated regulation of adenovirus gene expression by repression of mRNA accumulation. Mol. and Cell. Biol. 17:2207-2216, 1997.**

**Elkon, K., Liu, C.-C., Gall, J.G., Trevejo, J., Marino, M.W., Abrahamsen, K.A., Song, X., Zhou, J.-L. Old, L.J., Crystal, R.G., and Falck-Pedersen, E. TNF-α plays a central role in immune mediated clearance of adenoviral vectors. Proc. Nat. Acad. Sci. 94:9814-9819, 1997.**


*Molecular Biology*

# Diane Felsen, Ph.D.

## ADVANCES IN UROLOGIC RESEARCH

This laboratory is a multi-disciplinary laboratory in the Department of Urology, whose co-directors are Dr. Felsen and Dix P. Poppas, MD, Director, Division of Pediatric Urology. Among the current projects are the following:

*Investigating the pathophysiology of ureteral obstruction:* Unilateral ureteral obstruction [UUO] results in decreases in renal function and in renal fibrosis. Current studies are designed to understand the mechanism of fibrosis, with the goal of eventual pharmacologic or genetic manipulation. Two candidate targets are transforming growth factor-β [TGF-β ], a pro-fibrotic cytokine and nitric oxide [NO], which appears to be antifibrotic. We are presently studying the fibrotic response to UUO in rats in the presence of a TGF-β antibody and in mice which have the gene for the synthesis of NO deleted [iNOS knockouts].

*Investigating the pathophysiology of bladder outlet obstruction:* Deleterious changes in bladder function occur following bladder outlet obstruction. The focus of this research is on the role of the NO system in the normal and obstructed bladder, which we are studying using either pharmacological manipulation of NO or by using iNOS knockouts. We are also studying the role of elastin in the development of bladder compliance in both normal and obstructed bladder using transgenic mice, which overexpress elastin.

*Development of Alternative methods of Wound Closure and Minimally Invasive Surgery:* We have been involved in the development of biological solders, as alternatives to suture, and the use of lasers to effect wound closure in the presence of these solders. The use of laser-activated solders can surmount some of the problems inherent in sutured wounds, such as leakage and surgeon-to-surgeon variability. We are also involved in developing novel instrumentation for minimally invasive surgical procedures. The combination of advances in surgical instrumentation and methods of wound closure should significantly advance the field of minimally invasive surgery.

**RECENT PUBLICATIONS**


**Wright, E.J., McCaffrey, T.A., Robertson, A.P., Vaughan, E.D., Jr., and Felsen, D. Chronic unilateral ureteral obstruction is associated with interstitial fibrosis and tubular expression of transforming growth factor-β. Laboratory Investigation 74:528-537, 1996.**

**O'Connor, L.T., Jr., Vaughan, E.D., Jr., and Felsen D. In vivo cystometric evaluation of progressive bladder outlet obstruction in rats. J. Urol. 158:631-635, 1997.**


*Pharmacology*

# Donald A. Fischman, M.D.

## CELL AND DEVELOPMENTAL BIOLOGY OF MUSCLE

We are examining three interrelated projects on the differentiation of skeletal and cardiac muscle.

**Molecular genetic analysis of thick filament assembly.** In addition to myosin, thick filaments contain seven associated proteins. We have cloned and sequenced two of these: C-protein and 86kD protein. The amino acid sequences reveal that both proteins belong to the C2 subset of the immunoglobulin superfamily. Since members of this protein family bind and link cell surface-associated proteins, we are testing the hypothesis that immunoglobulin-like domains of C-protein and 86kD protein function in intracellular adhesive interactions. Recombinant sense and antisense constructs of these genes have been prepared to disrupt synthesis and function of these proteins during myofibril assembly in cultured muscle.

**Gene transfer in chicken embryos.** Techniques have been perfected for transplanting somites, containing precursor cells of skeletal muscle, from quail to chicken embryos. The grafted quail eggs exhibit normal development, but can be distinguished from the host (chicken) cells. Using replication-defective retroviruses we are stably introducing recombinant genes into quail somites for transplantation into chick embryos developing in ovo. At specific stages of development the embryos are analyzed for the phenotypic effects of transgene expression. Specific genes under analysis include the myosin heavy and light chains, C-protein, 86kD protein and desmin.

**Retroviral analysis of cardiac cell lineages *in vivo*.** The replication-defective retrovirus, CXL, expressing bacterial β-galactosidase, is used to tag cardiac precursor cells of early chick embryos. The integrated viral genes are transmitted to all daughter cells, marking the clonal derivatives of the originally infected parental cell. After microinjection of the vector into the cardiogenic mesoderm on the 1st through 3rd days of development, the hearts of hatched chickens are stained for β-gal expression and the positive clones analyzed in 3-dimension. We are defining the number of cell divisions cardiac myocytes completed during development, and establishing the variety of cell types which arise from a single cardiogenic precursor.

**RECENT PUBLICATIONS**


**Mikawa, T. and Fischman, D.A. The polyclonal origin of myocyte lineages. Ann. Rev. Physiology 58:509-21, 1996.**

**Gilbert, R., Kelly, M.G., Mikawa, T. and Fischman, D.A. The carboxyl terminus of myosin binding protein C (MyBP-C, C-protein) specifies incorporation into the A-band of striated muscle. Journal of Cell Science 109:101-111, 1996.**


*Cell Biology & Genetics*

*Neuroscience*

# Robert P. Fisher, M.D., Ph.D.

## MOLECULAR MECHANISMS OF CELL CYCLE CONTROL

The major events of the cell division cycle are triggered by the cyclin-dependent kinases (CDKs). Sequential activation and inactivation of CDKs ensures properly executed and ordered cell cycle transitions; derangement of the program can lead to errors in the duplication and segregation of chromosomes, and may contribute to oncogenic transformation. Thus, the activity of these enzymes is precisely controlled by both positive and negative regulators. Activation of a CDK requires binding of a cyclin and phosphorylation at a conserved threonine residue by a CDK-activating kinase (CAK). In mammalian cells, the major CAK is itself a CDK, composed of CDK7 and cyclin H. In addition to its role in cell cycle control, the complex of CDK7 with cyclin H and the assembly factor MAT1 participates in transcription by RNA polymerase II, as a component of the general transcription/DNA repair factor TFIIH.

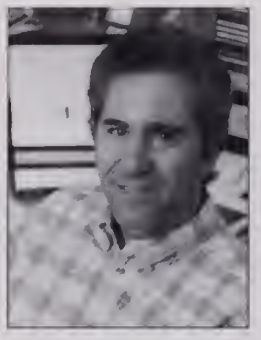
My laboratory uses biochemical and genetic approaches to determine the role of CDK7 complexes in driving the cell cycle. Intriguingly, the same CDKs that are targets for CAK can also activate CAK *in vitro*, suggesting that a positive feedback loop governs CDK activation. We are at present searching for kinases that activate CDK7 *in vivo*, both in mammalian cells and in yeast. We are also exploring a possible role for CAK in coordinating the cell cycle with transcription and DNA repair. A focus of these studies is MAT1, which may mediate association of CAK with TFIIH. We are introducting mutated versions of MAT1—for example, one lacting its amino-terminal RING finger zinc-binding domain — into cells, to discern a function, either in mediating protein-protein interactions between CAK and other regulators, or in localizing the complex to discrete subcellular compartments. We are also studying the interactions between a CDK7 homolog and the cell cycle machinery in the fission yeast, Schizosaccharomyces pombe, by a combination of genetics and biochemistry.

**RECENT PUBLICATIONS**


**Fisher, R.P., Jin, P., Chamberlin, H.M. and Morgan, D.O. Alternative mechanisms of CAK assembly require an assembly factor or an activating kinase. Cell 83:47-57, 1995.**

**Fisher, R.P. CDKs and cyclins in transition(s). Curr. Opin. Genet. Dev. 7:32-38, 1997.**


*Cell Biology & Genetics*



# Leonard P. Freedman, Ph.D.

## TRANSCRIPTIONAL CONTROL BY STEROID/NUCLEAR HORMONE RECEPTORS

My laboratory is studying the regulation of transcription by various members of the steroid/nuclear receptor superfamily, which includes receptors for glucocorticoids, the sex steroids (estrogen, progesterone, androgen), thyroid hormone, retinoic acid, and vitamin $D_3$. These intracellular receptors act as direct signal transducers in that they are able to both bind small ligands or steroids and associate with specific DNA elements; in the process they activate or repress the transcription of specific target genes.

The lab has two principal lines of research. First, we are actively exploring mechanistic aspects of receptor function leading to transcriptional control. We have described how the vitamin $D_3$ receptor (VDR) can act as both an activator and repressor of transcription, depending on the target gene and on which components of the transcription initiation apparatus the receptor is directly acting on. We recently isolated a novel coactivator complex of VDR that associates with the receptor in a ligand-dependent manner and is required to mediate transcriptional enhancement by VDR. Such coactivators may represent a critical component of nuclear receptor action that might confer cell-type specific effects of this signalling system.

A second focus of the lab is the identification of genes that are direct targets of these receptors, with a particular emphasis on how the regulation of such genes relates to known biological phenomena, such as vitamin $D_3$-induced differentiation or growth- suppression of cells of the immune system. We have succeeded in isolating several known and novel genes that appear to be both transcriptional targets of the vitamin $D_3$ receptor and act as key regulators of myeloid cell differentiation, including the cyclin-dependent kinase inhibitor $p21^{Waf1, Cip1}$, b-zip/HLH protein Mad-1, and a homeobox gene called HoxA10.

The lab's long-term goal is to combine the knowledge we are accumulating from these two areas of study, in order to more deeply interpret and perhaps ultimately manipulate the regulatory circuitry in effect within, for example, certain kinds of vitamin $D_3$-responsive leukemias, and perhaps breast and prostate cancers.

**RECENT PUBLICATIONS**


**Lemon, B.D., Fondell, J.D. and Freedman, L.P. Retinoid X receptor: vitamin D3 receptor heterodimers promote preinitiation complex formation and direct 1,25-dihydroxyvitamin D3-dependent cell free transcription. Mol. Cell. Biol. 17:1923-1937, 1998.**

**Rots, N.Y., Liu, M., Anderson, E.C. and Freedman, L.P. A differential screen for ligand-regulated genes: Identification of HoxA10 as a target for vitamin D3 induction in myeloid leukemic cells. Mol. Cell. Biol. 18:1911-1918, 1998.**


*Cell Biology & Genetics*

# Henry Furneaux, Ph.D.

## THE REGULATION OF GENE EXPRESSION AT THE POSTTRANSCRIPTIONAL LEVEL

We know considerable detail about how mRNA is transcribed, capped, polyadenylated, and spliced in the nucleus. In contrast, very little is known of the fundamental mechanisms that underlie the successful transport of a particular mRNA to the cytoplasm and its translation by ribosomes. It is clear, however, that this pathway is regulated by specific cis-acting sequences in the mRNA itself. One of the first of such sequences to be described was the Shaw-Kamen (or AU-rich ) element. These elements direct the selective and rapid turnover of mRNA. Thus, in unstimulated cells, mRNAs that contain these elements rapidly disappear. Upon stimulation, degradation is blocked by transacting factors and a rapid increase in steady state level is observed. We have found that the Elav-like RNA binding proteins ( HuD, HuC, Hel-N1 and HuR ) bind selectively to these elements and are the key transacting factors that mediate the stabilization of these mRNAs. Our working hypothesis is that the Elav-like proteins associate with mRNA in the nucleus and chaperone them to their cytoplasmic destination. Our future studies will focus on the mechanism of the Elav-like proteins and the other factors that activate them. The understanding of this pathway is not only of fundamental interest but is also directly relevant to disease. We originally identified the Elav-like protein as tumor antigens. HuR, in particular, is aberrantly expressed in a wide variety of human tumors. The glucose transporter (Glut1) and vascular endothelial growth factor (VEGF) are two important genes that are aberrantly upregulated by HuR in tumor cells. Thus, inhibitors of this pathway may provide novel anti-tumor agents.

The other major preoccupation of the lab is the study of mRNA splicing. Recent exciting observations from labs working in yeast have indicated that pre-mRNAs may be spliced by a novel mechanism involving a specific endonuclease and an RNA ligase. We are currently investigating whether this pathway also operates in animal cells.

**RECENT PUBLICATIONS**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**Levy, N.S., Chung, S., Furneaux, H.M. and Levy, A.P. Hypoxicstabilization of VEGF mRNA by the RNA-binding protein HuR. J.Biol.Chem. 273: 6417-6423, 1998.**


*Neuroscience*

# Daniel Gardner, Ph.D.

## NEURONAL DATABASES, NEURAL NETWORKS AND NEURONAL IDENTITY

Two fundamental questions of neuroscience define neuronal identity and coding of neuronal signals. Our laboratory is conducting a multi-year initiative to develop networked databases of brain neurophysiology that will allow exploring these questions. One database—funded by the NIMH's Human Brain Project—will include somatosensory cortical neurons and characteristic neurophysiological data encapsulating these neurons' responses to specific stimuli. A parallel NIH-funded effort is establishing a database of molluscan identified neurons and the largely intracellular electrophysiological data that describe them.

Neuron data will incorporate parameters used by neurophysiologists to describe recording methodology, stimulating paradigms, and electrophysiological responses. To make the database useful to brain neuroscientists, we are designing a suite of multiplatform tools supporting acquisition, query, and visualization of single and multi-electrode spike train datasets. These tools will allow integration of data characterizing responses of cortical neurons to complementary stimuli, synthesizing a unified understanding of brain information processing. With the resulting enhanced utilization of data, cortical experiments can be coordinated among laboratories, conserving valuable nonhuman primates. All data structures and methods defined in this project are designed to be generalizable to other electrophysiological studies in cortical and subcortical structures of the brain.

Our methodology includes development of object-oriented database schemas for neuronal data, as well as the use of Java, permitting databases to be accessible via the world-wide web to any member of the international neuroscience community using any contemporary computer system, including Macintosh, UNIX-XWindows, or MSWindows.

The project coordinates the efforts of brain researchers at NYU, Wash. U., the Krieger Mind/Brain Institute at Johns Hopkins, Yale, and Bowman Gray. Our collaborators at these institutions will aid development and testing of access and query methods and viewer tools and provide complementary physiological data from several techniques and preparations.

**RECENT PUBLICATIONS**


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**Abato, M., Tepel, M., Erde., S.M. and Gardner, D. A unified neurophysiology database storage schema for time series, histogram, and bivariate datasets. Soc. Neurosci., Abstr. 24: 134, 1998.**


*Physiology, Biophysics & Molecular Medicine*

*Neuroscience*

# James L. German, III, M.D.

## GENETIC ANALYSIS OF HUMAN ABNORMALITIES

Students in the Laboratory of Human Genetics develop strong intellectual bases in classical, human and molecular genetics, and in cell biology in general. In addition, they acquire a general understanding of the several areas of human genetics, (e.g. biochemical genetics, inborn errors of metabolism, human and medical cytogenetics, human dysmorphology and teratology, human molecular genetics and population genetics), simultaneously becoming aware of the associated ethical dimension of genetics when man himself is the species being studied.

The Laboratory's research utilizes techniques and methods in three areas: somatic cell (tissue culture) genetics, cytogenetics, and molecular genetics. In addition, persons and families affected with selected genetic disorders are seen in relation to the research, thereby providing a degree of clinical orientation to the work.

*Areas of research:* A major research effort at present concerns Bloom's Syndrome (BS), an autosomal recessively transmitted disorder that predisposes enormously to cancer of many types and sites. The genome of BS cells is remarkably unstable, and hypermutability doubtless explains the cancer proneness. The locus mutated in BS, BLM, which we mapped to chromosome band 15q26.1 using a powerful but, until now, little-used method for detecting linkage, namely homozygosity mapping has recently been isolated. Working out its "biology" probably will require, in addition to molecular genetics, the use of techniques for studying DNA synthesis and repair (DNA synthesis is disturbed in BS), protein chemistry, and yeast genetics. Other areas of research in which graduate students might work in this laboratory include: the molecular genetics of human sex chromosomes and human sexual development, and mechanisms of gene regulation employing the region of the genome in which is located XG, the structural gene for the XG blood group. XG was recently cloned in this laboratory and discovered to be partly in the pseudoautosomal region of the sex chromosomes, but extending into the strictly X-linked portion. XG is interesting as a model because it is co-regulated with a closely linked pseudoautosomal gene, MIC2.

**RECENT PUBLICATIONS**


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**Ellis, N.A., Groden, J., Ye, T.Z., Straughen, J., Lennon, D.J., Ciocci, S., Protycheva, M. and German, J. The Bloom's syndrome gene product is homologous to RecQ helicases. Cell 83:655-666, 1995.**


*Cell Biology & Genetics*

# Marvin C. Gershengorn, M.D.

## G PROTEIN-COUPLED RECEPTORS

The major focus of research in our laboratory group is to delineate the structure-function relationships of guanine nucleotide-binding (G) protein-coupled receptors (GPCRs). GPCRs regulate the function of virtually every cell in the body, are involved in some pathophysiologic processes and are the target site for therapeutic agents. We study two receptors that are activated by peptides, thyrotropin-releasing hormone (TRH), which is a tripeptide that regulates the anterior pituitary gland and acts in the central nervous system (CNS), and calcitonin, which is a 32-amino acid peptide that regulates bone metabolism and acts in the CNS also, and a third receptor (KSHV GPCR) that is encoded within the genome of a herpesvirus and may be involved in the pathogenesis of Kaposi's sarcoma and B-cell lymphomas. TRH and calcitonin bind to receptors on cell surfaces leading to activation of a heterotrimeric G protein(s) that in turn activates an effector enzyme, a phosphoinositide-specific phospholipase C or adenylyl cyclase, or both. Using complementary DNAs (cDNAs) that encode these receptors and techniques of molecular genetics, the structure-function relationships of hormone and antagonist binding to these receptors, coupling of the receptors to the G proteins, and mechanisms of regulation of receptor synthesis, internalization, desensitization, down-regulation and degradation are being studied. KSHV GPCR is a receptor that signals via the phosphoinositide-specific phospholipase C-inositol 1,4,5-trisphosphate-diacylglycerol cascade in the absence of an agonist, that is, KSHV GPCR is constitutively active. The pathobiology of KSHV GPCR and its role in the pathogenesis of two cancers is being explored. Emphasis is placed on the use of site-specific and chimeric receptor mutants, of delineation of the signaling cascades and their cellular responses, of hormone (agonist) and antagonist analogues, and on molecular modelling of ligand-receptor interactions.

**RECENT PUBLICATIONS**


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**Colson, A.-O., Perlman, J.H., Smolyar, A., Gershengorn, M.C. and Osman, R.: Static and dynamic roles of extracellular loops in G-protein coupled receptors: A mechanism for sequential binding of thyrotropin-releasing hormone to its receptor. Biophys. J. 74:1087-1100, 1998.**


*Physiology, Biophysics & Molecular Medicine*

*Cell Biology & Genetics*

# Filippo G. Giancotti, M.D., Ph.D.

## INTEGRIN SIGNALING

Upon binding to components of the extracellular matrix (ECM), the integrins interact with cytoskeletal and signaling molecules. Since normal cells need to adhere to the ECM in order to proliferate, we have focused on the signaling mechanisms which link integrins to the cell cycle machinery. It is important to examine these mechanisms because they are likely to contribute to the spatial regulation of cell proliferation during development and in the adult. In addition, neoplastic cells are no longer sensitive to the growth control exerted by the extracellular matrix, and this property is likely to contribute significantly to their ability to invade and metastasize.

We have found that, upon binding to the ECM, a class of integrins recruit the signaling protein Shc. Shc is an SH2-PTB domain adaptor which links various tyrosine kinases to Ras by recruiting the Grb2/mSOS complex to the plasma membrane. While Shc can bind directly to the tyrosine phosphorylated cytoplasmic domain of a6β4, the recruitment of Shc to other integrins is indirect and mediated by the interaction of their a subunit with caveolin-1 and thereby Fyn. Mutagenesis and dominant negative studies indicate that the association of specific integrins with Shc is necessary and sufficient to activate the Ras-Erk signaling pathway. The Shc pathway appears to be important for cell survival and proliferation because ligation of Shc-ativating integrins allows normal cells to progress through the G1 phase of the cell cycle in response to growth factors, while ligation of other integrins causes exit from the cell cycle and, in the absence of intercellular contact, apoptotic death.

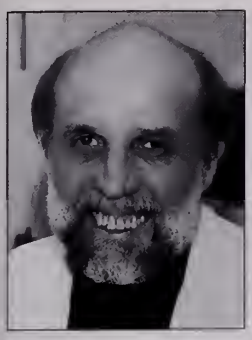
We are currently combining biochemical and molecular genetics methods to further study the membrane proximal events and signaling pathways activated by integrins and the mechanisms by which these pathways regulate cytoskeletal organization, survival, cell cycle progression, and differentiation.

**RECENT PUBLICATIONS**


**Wary, K.K., Mainiero, F., Isakoff, S., Marcantonio, E.E. and Giancotti, F.G. The adaptor protein Shc couples a class of integrins to the control of cell cycle progression. Cell 87:733-743, 1996.**

**Mainiero, F., Murgia, C., Wary, K.K., Curatola, A.M., Pepe, A., Blumemberg, M., Westwick, J.K., Der, C. and Giancotti, F.G. The coupling of a6-4 integrin to the Ras-MAP kinase pathways mediated by Shc controls keratinocyte proliferation. EMBO J. 16:2365-2375, 1997.**


*Cell Biology & Genetics*



# James Gibbs, M.D.

## PHYSIOLOGICAL MECHANISMS OF MOTIVATED BEHAVIOR

The physiological mechanisms which subserve motivated behavior are almost entirely unknown. To attack this general problem, we have focused on the regulation of food intake as a representative motivated behavior. In particular, we have been investigating the unidentified factors, activated by food ingestion, which produce satiety in animals and humans.

Following our originial report in 1979 and on the basis of subsequent studies, we have proposed that endogenous mammalian bombesin-like peptides (found in the gastrointestinal tract and brain) play important roles in satiety. The goal is to understand the functions of these peptides in the peripheral generation and in the central neural processing of the physiological satiety signals which serve to limit meal size and to regulate the length of the intermeal interval.

**RECENT PUBLICATIONS**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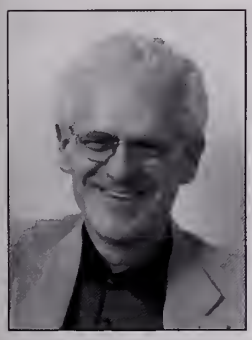
**Smith, J., S. Perez, P.A. Rushing, G.P. Smith, and J. Gibbs. Gastrin-releasing peptides 1-27 unlike bombesin, does not reduce sham feeding in rats. Peptides 18: 1465-1467, 1997.**


*Neuroscience*



# Gary Gibson, Ph.D.

## SIGNAL TRANSDUCTION AND OXIDATIVE PROCESSES IN NEURODEGENERATION

The primary aim of our research is to discover how altered signal transduction and oxidative processes lead to neurodegeneration and altered mental function. We examine directly aging Alzheimer's disease, hypoxia, aging, and a nutritional model that leads to chronic interruption of oxidative metabolism and to selective neurodegeneration (e.g., thiamine deficiency). Whether changes in signal transduction systems are the primary cause of the disease(s) and/or how they link the primary deficit or impaired oxygenation to altered gene expression, neurotransmitter release and abnormal brain function is being tested. The signal transduction systems that are being examined include: the phosphatidylinositide cascade (including protein kinase C), calcium (calcium transport, cytosolic free calcium and calcium compartments), cyclic AMP, mitochondrial and plasma membrane potentials, and the immediate early response genes such as *c-fos*.

A variety of *in vivo* and *in vitro* models and techniques are used to help elucidate the relation of abnormal oxygenation and signal transduction systems to brain dysfunction and neurodegeneration. Dynamic cell function is measured with fluorescent probes combined with imaging for cytosolic free calcium (at the cellular and subcellular levels) and membrane potentials (mitochondrial and plasma). Gene expression is evaluated by Northern blot analysis or *in situ* hybridization. Human brains from autopsy and cultured fibroblasts are employed for the studies of Alzheimer's disease. The research on aging utilizes cultured fibroblasts from humans and brains of aged animals both *in vivo* and *in vitro*. The hypoxia inquiries utilize rodent brains in vivo and in vitro. Hypoxia is also examined in cultured cells so that fluorescent probes and imaging can be used. The studies of thiamine deficiency utilize Western and Northern blot analysis, immunocytochemistry, *in situ* hybridization and histochemistry.

**RECENT PUBLICATIONS**


**Gibson, G.E., Toral-Barza, L. and Zhang, H. Selective hypoxia-induced changes in cell bodies and growth cones of NGF-differentiated PC12 cells. J. Neurochem. 69:603-611, 1997.**

**Calingasan, N.Y., Park, L.C.H., Calo, L.L., Trifiletti, R.R., Gandy, S.E., Gibson, G.E. Induction of nitric oxide synthase and microglial responses precede selective cell death induced by chronic impairment of oxidative metabolism. American Journal of Pathology 153:599-610, 1998.**


*Neuroscience*

# Eugene Golanov, M.D., Ph.D.

## CENTRAL NEURAL REGULATION OF CEREBRAL BLOOD FLOW (CBF)

Functional activation of the brain increases utilization of glucose and oxygen by neurons activated. Special neural system within the brain maintains CBF at the levels adequate to provide necessary oxygen and glucose levels. One of the key elements of this system is the area of medulla known as rostroventrolateral medulla (RVL). Excitation of RVL globally increases CBF playing a significant role in cerebral vasodilation in response to hypoxia. Vasodilatory pathways originating in the medulla ascend through the thalamic area to the cerebral cortex where they excite vasodilatory neurons that increase local cerebral blood flow.

Most of the aspects of functioning of brain blood flow regulatory system are unknown. We study this system by: (a) determining the RVL neurons initiating cortical vasodilation; (b) identifying the subcortical nuclei which mediate the elevations in rCBF evoked from RVL; (c) identifying the intracortical neurons which couples excitation of subcortical vasodilator pathway to cortical cerebrovasodialtion; and (d) analyzing cellular neuronal mechanisms of oxygen sensitivity.

Our long-term objectives are: to understand how the brain can protect itself from hypoxia and ischemia by increasing perfusion through activation of neural pathways. Our demonstration that the RVL is critical for the cerebrovascular to hypoxia may be critical not only to hypoxic stress but may protect the brain in stroke and trauma. The studies are highly relevant to an understanding of the neural mechanisms underlying the activation of rCBF in response to physiological and mental stimuli. Most of the brain imaging technologies currently use CBF as an index of neural events, yet still very little is understood about how the vascular dilatory signal is generated. The study may yield new insights into the pathways and mechanisms whereby the RVL, NTS, cerebellum, and visceral stimuli may influence cerebral cortical activity and hence mood, cognition, and/or behavior.

**RECENT PUBLICATIONS**


**Golanov, E.V. and Reis, D.J. Contribution of oxygen-sensitive neurons of the rostral ventrolateral medulla to hypoxic cerebral vasodilatation in the rat. J. Physiol. London 495: 201-216, 1996.**

**Golanov, E.V., Liu, F., and Reis, D.J. Stimulation of cerebellum protects hippocampal neurons from global ischemia. Neuroreport 9: 819-824, 1998.**


*Neuroscience*

# Jonathan D. Goldberg, Ph.D.

## PROTEIN STRUCTURE AND BIOPHYSICS

Our research is focused on the structural biology of signal transduction. Currently we are applying biochemical and biophysical methods, particularly X-ray crystallography, to study problems in two broad areas; firstly, the functions of protein kinases and lipid kinases in mitogenic signaling pathways, and secondly, proteins that detect and respond to DNA damage in eukaryotic cells.

Initial work addressed the structural basis of protein kinase regulation. We determined the crystal structure of a calmodulin-dependent protein kinase in John Kuriyan's laboratory at the Rockefeller University. The structure reveals how the kinase is regulated at the molecular level, and provides a firm basis for understanding the mechanistic roles of calmodulin-dependent kinases in the regulation of gene expression and cell proliferation.

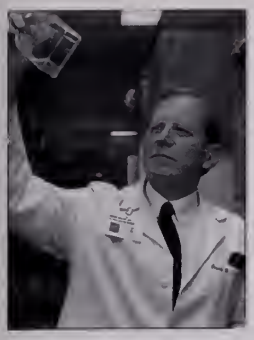
Building on this foundation, we are now pursuing detailed structural information on the family of lipid kinases related to phosphatidylinositol 3-kinase (PI3-kinase). Some members of the PI3-kinase family, such as the mammalian PI3-kinase catalytic subunit (p110), function in mitogenic signal transduction by phosphorylating inositol phospholipids, which serve as intracellular second messenger molecules. Surprisingly, other members of the PI3-kinase family have protein kinase activity (for example the DNA-dependent protein kinase), and these enzymes appear to have roles in DNA damage response and repair. We are focusing on a number of key structural questions: What common structural principles exist amongst the functionally diverse family of PI3-kinases? Can we rationalize in structural terms why some PI3-kinases phosphorylate inositol phospholipids while others will only phosphorylate protein substrates? Also, what is the structural basis for the molecular switch that activates the DNA-dependent protein kinase upon DNA binding? Answers to these and related questions will be sought using X-ray crystal structure determination of appropriate macromolecular complexes, testing of hypothesis using site-directed mutagenesis and biochemical studies to relate structure to function.

**RECENT PUBLICATIONS**


**Goldberg, J., Nairn, A.C., Kuriyan, J. Structural basis for the autoinhibition of calcium/calmodulin-dependent protein kinase 1. Cell 84:875-887, 1996.**

**Mossessova, E., Gulbis, J.M. and Goldberg, J. Structure of the guanine-nucleotide exchange factor Sec7 domain of human Arno and analysis of the interaction with ARF GTPase. Cell 92:415-423, 1998.**


*Biochemistry & Structural Biology*



# David W. Golde, M.D.

## MOLECULAR AND CELLULAR HEMATOLOGY

The Laboratory of Molecular and Cellular Hematology investigates the humoral regulation of normal and leukemic blood cell formation and the molecular mechanisms regulating transport through the facilitative hexose transporters. The biologic basis of colony-stimulating factor (CSF) action is studied at the level of receptor interaction, intracellular signaling, and transcriptional activation. We focus on the receptor for granulocyte-macrophage CSF (GM-CSF), particularly with respect to signaling through the alpha subunit and the biology of the soluble alpha subunit which arises by alternative splicing. We found that activation of the alpha subunit by GM-CSF leads to increased glucose transport through the glucose transporters, and we have a broad program investigating the properties of the facilitative hexose transporters with respect to the transport of various sugars, vitamin C, and other substrates in normal and malignant cells. We discovered the primary mechanism for vitamin C transport in human cells and the mechanism by which the brain obtains vitamin C. There are projects in the laboratory focused on the function of hexose transporters and monocarboxylate transporters in hematologic malignancy, HIV infection, and solid tumor models including breast cancer, prostate cancer, malignant melanoma, and colon cancer. We also study the role of oxidants and antioxidants in therapy-induced apoptosis in normal and malignant cells.

**RECENT PUBLICATIONS**


**Vera, J.C., Rivas, C.I., Velásquez, F.V., Zhang, R.H., Concha, I.I., and Golde, D.W. Resolution of the facilitated transport of dehydroascorbic acid from its intracellular accumulation as ascorbic acid. J. Biol. Chem. 270:23706-23712, 1995.**

**Heaney, M.L., Vera, J.C., Raines, M.A., and Golde, D.W. Membrane-associated and soluble granulocyte/macrophage colony-stimulating factor receptor α subunits are independently regulated in HL-60 cells. Proc. Natl. Acad. Sci. USA 92:2365-2369, 1995.**


*Pharmacology*

# Steven A. Goldman, M.D., Ph.D.

## NEURONAL PROGENITOR CELLS AND ADULT NEUROGENESIS

Our lab employs a cellular and molecular approach to the study of neuronal precursor cells and neurogenesis in adulthood. Using both avian and mammalian preparations, including the adult songbird brain, the rodent striatum and the human temporal lobe, we are examining the regulatory constraints on neuronal and oligodendrocytic production and migration in the adult brain. We are interested in the effects of discrete neurotrophic agents upon neuronal and oligodendroglial production by adult precursor cells. Related work employs transfection of isolated precursor cells with viruses bearing defined reporter genes, to follow the ontogeny and derivation of the newly generated neurons. We are transfecting ventricular cells *in vitro* with green fluorescent protein under the control of cell type-specific promoters, with later fluorescence-activated cell sorting, so as to isolate precursors. This approach allows us to assess not only lineage relationships, but also the extent to which the differentiation of single cells might be modulated by neurotrophic agents and matrix molecules. Our goal is to prepare precursors appropriate for implantation, while capitalizing on our nascent understanding of phenotypic specification to direct neuronal and oligodendrocytic differentiation by these adult progenitors. The lab is also interested in the cell types and molecules involved in neuronal migration into adult brain tissue. First, we are studying the specific role of cell adhesion molecule (CAM)-triggered, calcium-mediated signal transduction in regulating both neuronal departure from the ventricular zone, and fate during migration. To this end, we are using calcium imaging by confocal microscopy to study the role of both gonadal steroids and local paracrine agents in modulating the coupling of CAM expression to calcium signaling pathways. More broadly, we are investigating the interaction of radial cells, endothelial cells, and astrocytes in providing a permissive environment for neuronal migration. Our goal in all of this work is to induce neurogenesis and neuronal recruitment in nominally non-regenerative regions of the adult CNS, and to develop these recruitment strategies as therapeutic modalities.

**RECENT PUBLICATIONS**


**Wang, S., Wu, H., Jiang, W., Isdell, F., Delohery, F., Goldman, S. Isolation of neuronal precursors by sorting embryonic forebrain transfected with GFP driven by the T-alpha-1 tubulin promoter. Nature Biotechnol. 16:196-201, 1998.**

**Goldman, S., Luskin, M. Strategies utilized by migrating neurons of the postnatal vertebrate forebrain. Trends in Neurosci. 21:107-114, 1998.**


*Neuroscience*

# Bernice Grafstein, Ph.D.

## INFLUENCE OF THE EXTRACELLULAR ENVIRONMENT ON NEURONAL REGENERATION

Physiologically successful neuronal regeneration in the brain depends on the extracellular environment, which is regulated by the cerebrospinal fluid.

Damage to the brain and spinal cord usually results in a permanent disability, because neurons in the mammalian central nervous system regenerate very poorly, if at all. At present we are concentrating on the role of the extracellular environment in promoting axonal outgrowth, particularly with respect to the contribution of the pia-arachnoid to the composition of the cerebrospinal fluid, and how this may be influenced by the relationship between the pia-arachnoid and the brain parenchyma.

**RECENT PUBLICATIONS**


**(Grafstein, B. Axonal transport: function and mechanisms. In: "The Axon", edited by S.G. Waxman, J.D. Kocsis, and P.K. Stys. Oxford, New York. pp. 185-199, 1995.**

**Wang, J., Murray, M. and Grafstein, B. Cranial meninges of goldfish: age-related changes in morphology of meningeal cells and accumulation of surfactant-like multilamellar bodies. Cell Tiss. Res. 281: 349-358 (1995).**


*Neuroscience*

*Physiology, Biophysics & Molecular Medicine*

# Danielle Greenberg, Ph.D.

## PHYSIOLOGICAL MECHANISMS FOR THE SATIATING EFFECTS OF NUTRIENT FATS; GENETIC MODELS FOR OBESITY; PEPTIDES THAT MEDIATE FEEDING BEHAVIOR.

Ingestion of high fat diets is associated with serious public health problems. Numerous reports suggest that elevated intake of dietary fat, rather than total energy consumption, promotes weight gain. In order to control intake of fatty foods effectively, the physiological mechanisms which limit fat intake must be understood. We are engaged in research to identify these mechanisms in Sprague Dawley rats and in lean and genetically obese Zucker rats, a rodent model of obesity characterized by high intake of fat. Experiments are underway to determine to what extent physiological stimulation of the intestine by fats occurs during normal feeding and what effect such stimulation has on meal size by: (1) Determining the gastric emptying rate for different fats at the time these fats are being ingested; (2) Determining the effects on sham and real feeding of intestinal infusions of the lipid moieties determined to empty into the intestine during normal feeding when they are infused at rates determined to be physiological. Experiments are also underway to examine mechanisms that are involved in the control of meal size by intestinal fat infusions in real and sham feeding paradigms to; (3) Determining if brain regions involved in mediating the control of meal size are the same for real and sham feeding by use of c-Fos immunohistochemistry in Sprague-Dawley and lean and obese Zucker rats; and (4) Determining if vagal and cck mechanisms found to mediate intestinal satiety in sham feeding are also activated during real feeding.

**RECENT PUBLICATIONS**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*Neuroscience*

# Steven S. Gross, Ph.D.

## NITRIC OXIDE SIGNALING IN MAMMALIAN CELLS

Nitric oxide (NO) is a fascinating inter- and intra-cellular signaling molecule which had gone unrecognized until 1987. We now appreciate that NO mediates critical roles in key processes as diverse as the regulation of vascular tone and blood pressure, neuronal signaling, host-defense, and stimulation-secretion coupling. Work is underway to identify novel molecular mechanisms and targets for NO in physiological and pathophysiological settings. Our research uses molecular approaches to explore NO synthesis and action in cells. A major emphasis is on utilizing our emerging knowledge of NO biology for therapeutic benefit. NO is produced by NO synthases (NOSs), a family of 3 related proteins that differ in structure, function, distribution, and regulation. Although NOS isoforms are products of discrete genes, all catalyze an identical reaction in which L-arg yields NO and L-citrulline, at the expense of NADPH, O2, and water.

We are interested in synthetic mechanisms involved in this reaction and molecular events which regulate the expression of NOS mRNAs, proteins, and enzymatic activities. Additionally, we are exploring how ancillary genes influence the capacity of a cell to produce NO. These genes include those encoding enzymes involved in arginine metabolism and production of NO synthase cofactors.

Septic shock is the leading cause of death in ICUs in the U.S., afflicting 250-350 thousand annually with mortality estimates ranging from 40%-60%. Our research has led to the concept that a key step in sepsis is the induction by LPS and cytokines of the gene encoding a specific isoform of NOS that produces unregulated and toxic quantities of NO. Since NO is a potent vasodilator, its overproduction can lead to profound vasodilation, vascular collapse, and death. Accordingly, a variety of approaches have been developed to downregulate NO overproduction in septic patients; some are currently under clinical investigation.

**RECENT PUBLICATIONS**


**Salerno, J.C., Harris, D.E., Irizarry, K., Patel, B., Morales, A.J., Smith, S.M.E., Martasek, P., Roman, L.J., Masters, B.S.S., Jones, C.L., Weissman, B.A., Liu, Q., and Gross, S.S. A unique autoinhibitory control element functionally defines nitric oxide synthase isoforms. J. Biol. Chem. 272:29796-29804, 1997.**

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*Biochemistry & Structural Biology*

*Pharmacology*

# Lorraine J. Gudas, Ph.D.

## RETINOID PHARMACOLOGY: CELL GROWTH, DIFFERENTIATION, AND CANCER

Retinoids, which include both natural and synthetic derivatives of vitamin A, have a variety of effects on normal-cell differentiation and on the process of carcinogenesis. The response of many cell types to retinoid treatment is mediated initially by intracellular retinoid receptors and involves changes in gene expression, cell growth, and cell differentiation. This laboratory is studying how retinoids elicit these dramatic changes in cells through the identification and analysis of the genes which are regulated by retinoids. Some of these genes include homeobox genes, genes which encode transcription factors important in embryonic development. We have identified a retinoic acid responsive "enhancer," or DNA control region, 3' of one homeobox gene called Hoxa-1. We have shown that this enhancer regulates expression of the Hoxa-1 gene in response to retinoic acid both in cultured cells and in transgenic mice. We are now in the process of generating mice in which this enhancer is relocated to a more 5' position by gene targeting so that the functions of this retinoid-regulated enhancer can be studied in a mouse model.

Other projects in the laboratory include the analysis of the expression and functions of the intracellular retinoid binding proteins CRABP-I and CRABP-II, the study of the effects of the cyclic AMP signaling system on retinoid regulated genes, the study of various retinoid analogs in human oral squamous cell carcinomas (epithelial tumors of the head and neck), and the identification of new retinol (vitamin A) metabolites in specific cell types such as epithelial and neuronal cells. Collectively, these studies should lead to new insights into the roles of retinoids in the regulation of cell growth and to new treatments for diseases such as cancer and dermatological conditions such as acne, psoriasis, and skin wrinkling due to sun damage or aging.

**RECENT PUBLICATIONS**


**Langston, A.W., Thompson, J.R., and Gudas, L.J. Retinoic acid responsive enhancers located 3' of the Hox A and Hox B homeobox gene clusters: Functional analysis. J. Biol. Chem. 272:2167-2175, 1997.**

**Guo, X. and Gudas, L.J. Metabolism of All-*Trans* Retinol in normal human cell strains and squamous cell carcinoma lines from the oral cavity and skin: Reduced esterification of retinol in SCC lines. Cancer Research 58:166-176, 1998.**


*Molecular Biology*

*Pharmacology*

# Barry M. Gumbiner, Ph.D.

## CELL ADHESION AND MORPHOGENESIS

Our research concerns the functions of cadherin cell adhesion molecules and the associated cytoplasmic catenins in the morphogenesis of tissues.

β-catenin participates in the transduction of developmental signals. As part of the Wnt signaling pathway, β-catenin mediates a patterning event in the *Xenopus* embryo, the induction of dorsal-ventral polarity. Ectopic expression of β-catenin in the ventral side of the early embryo induces the duplication of axial structures, including the neural tube, head, and eyes. β-catenin translocates into the nucleus and regulates the expression of specific target genes. Nuclear import of β-catenin occurs by a novel mechanism and appears to be regulated by the Wnt signaling pathway. β-catenin nuclear import and signaling are regulated by an interesting complex of proteins, which contains the APC tumor suppressor protein, and a novel protein called Axin. Cadherins antagonize β-catenin signaling, because they bind β-catenin at the plasma membrane and sequester it away from the cytoplasmic/nuclear signaling pool.

Regulation of the adhesive functions of cadherins at the cell surface is also important for morphogenesis. A Xenopus cadherin, called C-cadherin, controls tissue movements through gastrulation. A process called convergence and extension, which causes the elongation of a tissue, is induced by members of the TGF family of growth factors, such as Activin. The adhesive function of C-cadherin is decreased in response to Activin, and this regulation of C-cadherin is required for tissue elongation.

Molecular studies of C-cadherin function provide insight into the mechanism of cadherin regulation. The functionally active form C-cadherin is a homodimer, and clustering of C-cadherin at the cell surface controls the strength of cell adhesion. A protein called p120-catenin interacts with the cadherin cytoplasmic tail and may regulate cadherin clustering and adhesion. The mechanisms by which p120, the other catenins, and other cytoplasmic effector proteins regulate cadherin adhesion is being investigated.

**RECENT PUBLICATIONS**


**Fagotto, F., Gluck, U. and Gumbiner, B.M. Nuclear localization signal-independent- and importin/karyopherin-independent nuclear import of β-catenin. Current Biology 8:181-190, 1998.**

**Yap, A.S., Niessen, C.M. and Gumbiner, B.M. The juxtamembrane region of the cadherin cytoplasmic tail supports lateral clustering, adhesive strengthening and interaction with p120ctn. J. Cell Biol., (in press), 1998.**


*Cell Biology & Genetics*

# David P. Hajjar, Ph.D.

## NITRIC OXIDE-EICOSANOID BIOCHEMISTRY

Nitric oxide (NO) is a product of the cytokine-activated cells. As is the case with eicosanoids, it appears that NO is an important second messenger which mediates vasodilation of arteries and inhibits cell growth. We have now begun studies to determine the relationships between NO generation and its interaction with other second messengers in the context of signal transduction in atherosclerosis. Since NO production is altered in *in vivo* models of atherosclerosis, we tested the hypothesis that CE would alter smooth muscle cell-generation of NO. We discovered that smooth muscle cells do not possess constitutive NOS activity, but could be activated to generate NO by increased transcription of an inducible NOS (iNOS). In addition, the presence of unsaturated CE upregulates cytokine-induction of iNOS by increasing transcription of its mRNA. The mechanisms by which this occurs are presently being investigated.

Interestingly, NO has been shown to interact with heme-containing proteins, such as myoglobin, hemoglobin, and guanylate cyclase. Since COX-1 is a heme containing enzyme, it is also possible that NO could alter COX-1 catalytic activity. Literature in this area is contradictory, as both stimulation and inhibition of COX-1 activity have been observed. We have recently shown that NO stimulates COX-1 activity by a heme-independent mechanism. We now postulate that NO alters the secondary structure of the protein by oxidation and nitrosothiol formation of a critical sulfhydryl group necessary for the attachment of a non-catalytic (but potentially negative allosteric) domain in the major active cleft of the enzyme. This observation is significant since it will be the first time that nitrosothiol formation by NO leads to activation (not inhibition of an enzyme), and by a mechanism which will lead to the elucidation of the function of a subdomain of this protein. By using a variety of mutational analyses, we are defining the role of the putative negative allosteric domain, and specific cysteine residues believed to be important in NO-induction of COX-1 activity. In addition, these experiments will be performed using reconstitution assays with defined lipids. Lipids will be extracted from the membranes of normal and CE-enriched cells to determine the influence of lipid modification on catalytic activity of COX-1, which is a membrane-associated protein. Because the coordinates of the crystal structure of COX-1 are now available, we will also use computational chemistry to first model the interactions that we have observed in the laboratory, and then to make predictions as to the exact mechanisms by which the enzyme functions in the presence of NO and cholesterol.

**RECENT PUBLICATIONS**


**Pomerantz, K.B., Summers, B.D., Lander, H.M., Hajjar, D.P. G-protein-mediated signalling in cholesterol-enriched arterial smooth muscle cells: I. Reduced membrane-associated G-protein content due to diminished isoprenylation of G γ-subunits and p21 ras. Biochemistry, 36: 9523-9531, 1997.**

**Pomerantz, K.B., Summers, B.D., Hajjar, D.P. G-Protein mediated signaling in cholesterol-enriched arterial smooth muscle cells: II. G-Protein-dependent eicosanoid regulation by protein kinase C-δ. Biochemistry, 36: 9532-9539, 1997.**


*Biochemistry & Structural Biology*

# Katherine A. Hajjar, M.D.

## MOLECULAR BIOLOGY OF ENDOTHELIAL CELL FUNCTION

Our laboratory applies techniques of cell and molecular biology to the study of endothelial cell function. Our ultimate goal is to understand how blood vessels form and how blood fluidity is controlled. We hope eventually to develop new strategies for the diagnosis and treatment of vascular disorders.

Endothelial cells participate in the control of vascular reactivity, cellular adhesion events, angiogenesis, and hemostasis. The fluid state of blood is regulated by several surface-connected endothelial cell systems that inhibit the deposition of fibrin or impair platelet reactivity. A primary interest in our laboratory is the receptor-mediated surface assembly of plasminogen and tissue plasminogen activator. At the cell surface, these proteins promote efficient generation of plasmin, the major thrombus-dissolving protease in blood. Annexin II is a cell surface receptor that mediates this assembly and promotes plasminogen activation at the blood vessel wall. In addition, we are examining the role of this assembly system in angiogenesis, the formation of new blood vessels. Finally, we are studying the effects of the prothrombotic, thiol-containing oxidant, homocysteine, on endothelial cell function.

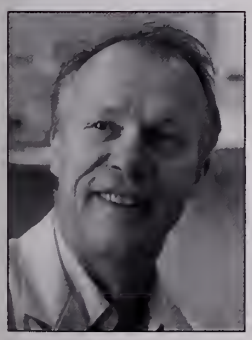
Our present studies focus on [1] structure function analysis of the molecular interactions that promote assembly of annexin II, plasminogen, and tissue plasminogen activator; [2] regulation of annexin II expression by endothelial cells, myeloid cells, and macrophages; [3] the role of plasminogen activation in settings of new blood vessel formation; and [4] host defense mechanisms to homocysteine-induced oxidant stress. These studies employ a wide variety of *in vitro* and *in vivo* methods including molecular cloning and expression techniques, protein purification procedures, gene transcription assays, and *in vivo* models of angiogenesis.

**RECENT PUBLICATIONS**


**Hajjar, K.A., C.A. Guevara, E. Lev, K. Dowling, and J. Chacko. Interaction of the fibrinolytic receptor, annexin II, with the endothelial cell surface: Essential role of endonexin repeat II. J. Biol. Chem., 271:21652-21659, 1996.**

**Hajjar, K.A., L. Mauri, A. Jacovina, F. Zhong, U.A. Mirza, J.C. Padovan, B.T. Chait. Tissue plasminogen activator binding to the annexin II tail domain: Direct modulation by homocysteine. J. Biol. Chem., 273: 9987-9993, 1998.**


*Cell Biology & Genetics*



# Ulrich Hammerling, Ph.D.

## IMMUNOCHEMISTRY

Vitamin A has a profound impact on several physiological processes in development and adult life, including the immune system, hence our interest in this molecule. Best described as a prohormone, vitamin A works by a number of activated forms, or metabolites, each fulfilling specialized functions: Retinaldehyde is the universal chromophore in vision, and retinoic acid is closely associated with cell differentiation and morphogenesis. A third class of retinoids was discovered in our laboratory which are involved in the control of cell proliferation. These are the retro-retinoids, 14-hydroxy-retro-retinol (14HRR; acting as a growth agonist) and anhydro-retinol (AR; an antagonist), and the normal retinoid, 13,14-dihydroxy-retinol (DHR; also a growth agonist).

In contrast to the mechanism of action of retinoic acid for which a nuclear mechanism has been defined, the retro-retinoids and DHR appear to function by a cytoplasmic mechanism. Although the receptor(s) for these retinoids have as yet to be defined, their existence has been inferred and their location assigned to the cytoplasm. The arguments rest in part, on the findings that AR induces apoptosis in a number of cell lines. Since this effect is reversible by 14HRR (by receptor competition), AR and 14HRR may bind to the same receptor. The AR-mediated cell death is not affected by pharmacological blockers of protein or RNA synthesis, and hence nuclear events are excluded as the primary cause of programmed cell death. Furthermore, certain blockers of signal transduction kinases can prevent apoptosis, strengthening the argument that the primary receptors for AR/14HRR are cytoplasmic and allied with signal transduction events. The straight-forward interpretation is that they are kinases themselves, and if this hypothesis can be proven in the coming years, an entirely new and exciting paradigm will be born.

**RECENT PUBLICATIONS**


**Buck, J., Grun, F., Kimura, S., Noy, N., Derguini, F., Hammerling, U. Anhydroretinol: A naturally occurring inhibitor of lymphocyte physiology. J Exp. Med. 178:675-680, 1993.**

**Derguini, F., Nakanishi, K., Hammerling, Y., Chua, R., Eppinger, T., Levy, E., Buck, J. 13, 14-Dihydroxy-retinol, a new bioactive retinol metabolite. J Biol Chem. 270:18875-18880, 1995.**


*Immunology*

# Hugh C. Hemmings, M.D., Ph.D.

## NEUROPHARMACOLOGY OF GENERAL ANESTHETICS

Elucidation of the molecular mechanisms by which general anesthetics act is an important goal in neuropharmacology which is necessary for the development of safer and more specific anesthetic agents. Electrophysiological evidence indicates that general anesthetics act primarily on synaptic transmission without affecting axonal conduction or neuronal excitability. At clinically relevant concentrations, most general anesthetics depress excitatory synaptic transmission, while some, including propofol and barbiturates, facilitate inhibitory synaptic transmission. There is good evidence for both presynaptic and postsynaptic mechanisms for these effects, including presynaptic reductions in excitatory neurotransmitter release, inhibition of postsynaptic responses to excitatory neurotransmitters, and facilitation of postsynaptic responses to inhibitory neurotransmitters. The precise molecular mechanisms involved in these effects are unknown.

Experiments to probe the presynaptic effects of anesthetics employ a functional subcellular model of the synapse (synaptosomes), as well as purified components of the major presynaptic phosphorylation systems. The effects of various general anesthetics on depolarization- or secretagogue-induced neurotransmitter release (e.g., glutamate, GABA, norepinephrine, dopamine, neuropeptides) and on changes in the phosphorylation of specific presynaptic proteins involved in the control of neurotransmitter release are being studied in synaptosomes. The effects of anesthetics on the activities of purified protein kinases and protein phosphatases, and on the phosphorylation and dephosphorylation of purified synaptic proteins by their appropriate purified kinases and protein phosphatases are being studied.

We are also interested in the basic biochemical mechanisms involved in the regulation of protein phosphatase activity in neurons. Previous studies have identified an endogenous neuronal protein phosphatase inhibitor that is an important molecular integrator of multiple converging cellular signals in dopaminoceptive neurons. This protein, known as DARPP-32 (dopamine- and cAMP-regulated phosphoprotein, Mr=32,000), has been extensively characterized and is being used to study the regulation of protein phosphatase-1 activity in cells. We are attempting to identify specific targeting subunits for protein phosphatase-1 in neurons.

**RECENT PUBLICATIONS**


**Hemmings, H.C. Jr. and Adamo, A.I.B. Effect of halothane on conventional protein kinase C translocation and down-regulation in rat cerebrocortical synaptosomes. Br. J. Anasth. 78:189-196, 1997.**

**Ratnakumari, L. and Hemmings, H.C. Jr. Effects of propofol on sodium channel-dependent sodium influx and glutamate release in rat cerebrocortical synaptosomes. Anesthesiology 86:428-439, 1997.**


*Pharmacology*

# Barbara L. Hempstead, M.D., Ph.D.

## NEUROTROPHIC GROWTH FACTORS

The primary aims of our research is to define the mechanism of action of a family of growth factors, the neurotrophins. Although classically defined as factors promoting the survival and differentiation of neurons, these growth factors are now recognized as modulating neuronal function postnatally, and in regulating the development of nonneuronal organs, such as the cardiovascular system. We are using molecular and cell biological techniques to address the question of specificity of neurotrophin growth factor action. We are addressing questions about how the interaction of neurotrophins with their receptors result in a diversity of biological function such as neuritogenesis, neural crest survival, vascular smooth muscle cell migration. Are distinctive signal transduction pathways activated in different cell types, or at different developmental stages? We are utilizing both *in vito* and mouse null mutant models to address these questions through analysis of neurotrophin receptor function, of modulation of signal transduction pathways, and of transcriptional regulation which influence the diverse biological outcomes.

**RECENT PUBLICATIONS**


**Donovan, M.J., Hahn, R., Tessarollo, L., and Hempstead, B.L. Identification of an essential nonneuronal function of neurotrophin 3 in mammalian cardiac development. Nature Genetics 14:210-213, 1996.**

**Teng, K.K., Courtney, J.C., van Bergen en Henegouwen, P., Birge, R.B., and Hempstead, B.L. Dissociation of NGF induced signal transduction from neurite elongation by expression of a mutant adaptor protein v-Crk in PC12 cells. Molecular and Cellular Neuroscience 8:157-170, 1996.**


*Neuroscience*

# Doris Herzlinger, Ph.D.

During embryonic development a population of dispersed, spindle-shaped cells called intermediate mesoderm matures into the epithelial tubules of the kidney. The focus of my research program is to characterize the molecular regulation of this process. Recent studies in the laboratory demonstrate that a single gene, *Wnt*, triggers intermediate mesoderm to convert into kidney tubules *in vitro*. Interestingly, this gene is the homologue of a Drosophila gene, *wingless*, that mediates body organization during fly development. Studies are in progress to define the cellular mechanisms by which *wnt* genes act in developing mammalian renal tissues. Additional studies address the pathway by which diverse renal cell types arise from intermediate mesoderm. Using molecular biological techniques to tag single cells of this embryonic primordium, we show that early in development a single cell can give rise to diverse kidney tubular cell types. Moreover, we have identified the time at which embryonic renal cells become committed to maturing into a single cell type. These findings make renal development an exciting model system to address one of the major questions of cell and molecular biology today: What are the mechanisms that direct embryonic cells to differentiate into unique, mature cell types?

**RECENT PUBLICATIONS**

**Barasch, J., Qiao, J. and Herzlinger,D. Multiple Ureteric Bud Growth Factors including FGF-2 Support Renal Stem Cell Proliferation. American Journal of Physiology 273: F757-F767, 1997.**

*Physiology, Biophysics & Molecular Medicine*

# Joy Hirsch, Ph.D.

## FUNCTIONAL MAGNETIC RESONANCE IMAGING

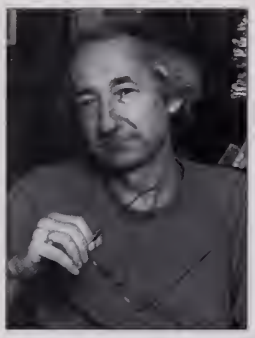
Conventional imaging of the brain can be enhanced to include information about the function of the brain due to the recent discovery that magnetic resonance imaging (fMRI), has created a challenging new opportunity to map and understand human brain function. The fMRI laboratory at MSKCC is one of the few centers in the country with this capability. Efforts to explore human brain organization have yielded new insights into questions such as how visual objects are recognized by the brain and how second languages are represented, as well as a transference of benefits to patient care especially in neurosurgical planning.

**RECENT PUBLICATIONS**

**Hirsch, J., DeLaPaz, R.L., Relkin, N.R., Victor, J., Kim, K., Borden, P., Lee, K.M., Li, T., Rubin, N., and Shapley, R. Human visual processes involved in stereo and illusory contour-defined images are predominantly located in right occipital cortex using functional magnetic resonance imaging (fMRI). Society for Neuroscience, 21: 18, 1995.**

**Hirsch, J., DeLaPaz, R.L., Relkin, N.R., Victor, J., Kinm,K., Li, T., Rubin, N., and Shapley, R. Illusory contours activate specific regions in human visual cortex: evidence from functional magnetic resonance imaging, Proceedings of the National Academy of Sciences, 92: 6469-6473, 1995.**

*Neuroscience*



# William K. Holloman, Ph.D.

## DNA REPAIR MECHANISMS

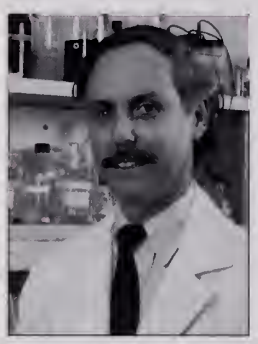
An important issue in genetic fidelity is DNA repair. Maintenance of the integrity of the genome and successful transmission of a full and intact complement of chromosomes from one generation to the next requires cellular systems that survey DNA for irregularities, repair problems, and coordinate repair with progression of the cell cycle. We study two genes in a model yeast system that contribute to the DNA repair capacity of the organism. One gene appears to encode a protein that serves in cell-cycle checkpoint control and DNA mismatch repair. The other appears to function in scanning for DNA sequence homology and thus can provide a correct template for repairing a damaged copy of the same gene. Genetic and biochemical analyses of the genes and their encoded proteins are under investigation with the goal of elucidating the mechanisms of action.

**RECENT PUBLICATIONS**


**Onel, K., Koff, A., Bennett, R.L., Unrau, P., and Holloman, W.K. The REC1 gene of *Ustilago maydis*, which encodes a 3'›5' exonuclease, couples DNA repair and completion of DNA synthesis to a mitotic checkpoint. Genetics 143:165-174, 1996.**

**Ferguson, D.O. and Holloman, W.K. Recombinational repair of gaps in DNA is asymmetric in *Ustilago maydis* and can be explained by a migrating D-loop model. Proc. Natl. Acad. Sci. USA 93:5419-5424, 1996.**


*Molecular Biology*



# Alan N. Houghton, M.D.

## SOLID TUMOR IMMUNOLOGY

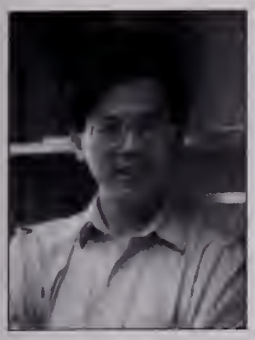
The objective of our laboratory is the study of the pathogenesis and host response to cancer. Studies from our lab and others have shown that the immune response to cancer is directed largely towards self antigens. The finding that immune recognition of cancer is directed largely against self antigens raises the issue of immunological tolerance. We are investigating how the immune system regulates recognition of self on cancer cells, and are using this as a model for understanding regulation of immune tolerance to self antigens. These studies involve the identification and biochemical characterization of cell surface and intracellular molecules in human and mouse cancer cells. Antigens have been identified that are recognized by the immune system. We are investigating immune recognition of two types of antigens. The first are tissue-specific differentiation antigens. Immune recognition of these antigens creates a type of autoimmunity that can lead to rejection of tumors. Initial indications are that immune recognition of tumors versus normal tissues can be distinct. The second group of antigens are mutated proteins, particularly oncoproteins that play a role in the pathogenesis of cancer. A number of strategies are being pursued to overcome immune tolerance. We have found that immunization with altered self proteins can induce immune responses against tissue-specific differentiation antigens. These maneuvers break immune tolerance. Secondly, we are exploring methods for genetic immunization, using DNA vaccines that can sort to different antigen presenting compartments within the cell. Thirdly, we are using genetic vectors, including adenovirus and retrovirus vectors, to introduce gene encoding antigens into professional antigen presenting cells, e.g. dendritic cells. These investigations and other strategies are being pursued to understand the role of immune tolerance in interfering with immune recognition of cancer and strategies to break tolerance. These studies have implications for development of cancer vaccines and other strategies for immunization against cancer.

**RECENT PUBLICATIONS**


**Naftzger, C., Takechi, Y., Kohda, H., Vijayasaradhi, S., and Houghton, A.N. Immune response to a differentiation antigen induced by altered antigen: a study of tumor rejection and autoimmunity. Proc. Nat. Acad. Sci. USA. 93:14809-14814, 1996.**

**Clynes, R., Takechi, Y., Moroi, Y., Houghton, A., and Ravetch J.V. Fc receptors are required in passive and active immunity to melanoma. Proc. Natl. Acad. Sci. USA. 95:652-656. 1998.**


*Immunology*



# Xin-Yun Huang, Ph.D.

## SIGNAL TRANSDUCTION

Our research focuses on the signal transduction by heterotrimeric G proteins. Of the various transmembrane signal transduction pathways, none is more widely used than those which involve seven-helix transmembrane receptors coupled to effector enzymes and ion channels through G proteins.

1) Direct stimulation of tyrosine kinases by G proteins: Recently our lab has discovered that certain nonreceptor tyrosine kinases can be direct effectors of G proteins. We have shown that the a subunit of Gq protein can directly stimulate the activity of Bruton's tyrosine kinase, whose defects are responsible for X chromosome-linked agammaglobulinemia in humans and X chromosome-linked immunodeficiency in mice. We are in the process examining the detail activation mechanism. Also, we are working on the newly identified direct effectors (a tyrosine kinase and a Ras-GAP) of the a subunit of G12 protein.

2) Genetic and biochemical dissection of the vertebrate G-protein-MAPK pathways: The mitogen-activated-protein kinase (MAPK) cascades (ERK, JNK, and p38) have been implicated in cell growth, proliferation, differentiation, transformation, apoptosis and many other cellular functions. Although activation of the ERK MAPK pathway by receptors with tyrosine kinase activity is well defined, the mechanisms used by G-protein-coupled receptors to activate these MAPK pathways in vertebrates remain to be elucidated. Using a combination of genetic and biochemical approaches, we are studying how G proteins are linked to these MAPK cascades.

3) Regulation and function of ion channels: Ion channels are essential for controlling the excitability of nerve, muscle, and other cell types. The behavior of ion channels can be modulated by G-protein-coupled neurotransmitter receptors. We are studying the signaling pathways by which G-protein-coupled neurotransmitter receptors modulate ion channel function. Also, we are developing strategies to design specific ion channel blockers.

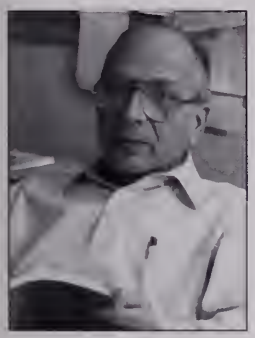
**RECENT PUBLICATIONS**


**Wan, Y., Kurosaki, T., and Huang, X.-Y. Tyrosine kinases in activation of the MAP kinase cascade by G-protein-coupled receptors. Nature 380: 541-544, 1996.**

**Bence, K., Ma, W., Kozasa, T., and Huang, X.-Y. Direct stimulation of Bruton's tyrosine kinase by Gq-protein a-subunit. Nature 389: 296-299, 1997.**


*Neuroscience*

*Physiology & Biophysics*



# Jerard Hurwitz, Ph.D.

## NUCLEIC ACID BIOCHEMISTRY

The replication of chromosomal DNA both in humans and *Schizosaccharomyces pombe* is under investigation. Both systems depend upon the combined action of the origins-recognition complex (a complex of 6 proteins) and a number of proteins that interact with this complex (including Cdc6 and the Mcm proteins). Activation of the origin region of DNA is followed by the formation of other complexes which include replication accessory proteins (polymerases, helicase, primase, etc.) that are essential for the initiation and elongation of DNA chains.

The goal of our laboratory is to examine the biochemical mechanisms involved in all stages of replication and to understand the function of the protein machinery. At present we are studying the roles played by RFC and PCNA, the eukaryotic clamp loader and clamp, respectively, that contribute to processive DNA synthesis catalyzed by DNA polymerase $\delta$ and $\varepsilon$ leading to the elongation of initated DNA chains. For these purposes, we have cloned and expressed the individed subunits that constitute RFC and DNA polymerase $\delta$. Reconstitution of all of the enzymatic activities of RFC with all five subunits has been accomplished. Similar studies with the distinct 5 subunits of *S. pombe* DNA polymerase $\delta$ are under investigation.

The cell cycle plays a key role in regulating DNA replication. A number of the proteins directly involved in DNA replication (RFC and DNA polymerase $\varepsilon$) have been shown to act as important sensors of DNA damage and PCNA has been found to be a target of a number of growth arrest gene products (p21 and p57). These control mechanisms are under investigation.

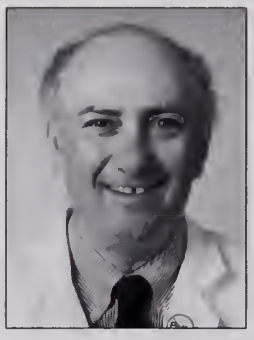
**RECENT PUBLICATIONS**


**Gibbs, E., Kelman, Z., Gulbis, J.M., O'Donnell, M., Kuriyan, J., Burgers, P.M.J., and Hurwitz, J. The influence of the PCNA-interacting domain of p21Cip1 on DNA synthesis catalyzed by the human and *Saccharomyces cerevisiae* polymerase $\delta$ holoenzymes. J. Biol. Chem. 272:2373-2381, 1996.**

**Zuo, S., Gibbs, E., Kelman, Z., Wang, T.S.-F., O'Donnell, M., MacNeill, S.A., and Hurwitz, J. DNA polymerase $\delta$ isolated from *S. pombe* contains five subunits. Proc. Natl. Acad. Sci. USA 94:11244-11249, 1997.**


*Biochemistry & Structural Biology*

*Molecular Biology*



# Charles E. Inturrisi, Ph.D.

## ANALGESIC PHARMACOLOGY

Dr. Inturrisi's research activities are directed toward the development of methods for the alleviation of pain. We are examining the molecular events at the receptor and signal transduction levels that underly the acute and chronic effects of opioid drugs. We have found that blockade of N-methyl-D-aspartate (NMDA) receptors prevents or reverses morphine tolerance in laboratory animals without altering the analgesic response. This separation of tolerance from analgesia allows for a systematic investigation *in vivo* and in cell culture of the changes in gene expression that occur with morphine tolerance. This strategy uses a combination of techniques for the measurement of RNAs and proteins including ribonuclease protection, Northern analysis, PCR, antisense knockdowns, and site-directed antibodies to identify and localize changes in receptors and signal transduction mediators. To complement and extend these approaches opioid tolerance, dependence and nociceptive behaviors will be measured in knockout mice engineered with an absent or mutated EAA receptor. At the behavioral level these studies have identified the NMDA receptor antagonists as lead compounds in the development of new drugs for use as nonopioid adjuncts to reduce morphine tolerance in pain patients. Therefore, we are also conducting clinical studies to evaluate the utility of these drugs in patients with pain. Thus, the ultimate goal of our research is to understand pain modulation and analgesia at the molecular and behavioral levels so as to maximize the therapeutic effects of analgesics while minimizing their adverse effects.

**RECENT PUBLICATIONS**


**Inturrisi, C.E.: Preclinical evidence for a role of glutamatergic systems in opioid tolerance and dependence. Sem. Neurosci. 9:110-119, 1997.**

**Shimoyama, N., Shimoyama, M., Elliott, K.J. and Inturrisi, C.E.: d-Methadone is antinociceptive in the rat formalin test. J. Pharmacol. Exp. Ther. 283:648-652, 1997.**


*Neuroscience*

*Pharmacology*

# Lionel B. Ivashkiv, M.D.

## CYTOKINES AND AUTOIMMUNITY

Cells of the immune system, such as T cells, B cells, and macrophages, are inappropriately activated in autoimmune and inflammatory diseases. The activation, growth, differentiation, and survival of these immune cells are regulated by cytokines, secreted proteins that activate gene expression. The activity of cytokines is mediated, in large part, by a major signal transduction pathway that utilizes Janus protein tyrosine kinases (Jaks) and STAT transcription factors. The goals of the laboratory are to determine the role of cytokines and STATs in human autoimmune and inflammatory diseases, and in animal models. We are also analyzing molecular mechanisms of inhibition of the Jak-STAT pathway that will identify novel approaches to inhibiting cytokine action in the treatment of inflammation. We have found that Stat3 is constitutively active in inflammatory arthritis, and the major activator of Stat3 is interleukin-6 (IL-6). IL-6 is critically important in the pathogenesis of rheumatoid arthritis and the collagen-induced arthritis animal model. We plan to investigate the role of Stat3 in inflammation using a combination of dominant negative mutants and gene targeting in mice and in human joint tissue grown as an explant in scid mice. The activation of Stat3 by IFNa and Stat5 by IL-2 are modulated by antagonistic cytokines (such as IL-4) during T-cell differentiation, and by crosslinking the T cell receptor during activation-induced cell death. The molecular mechanisms of modulation of Jak-STAT signaling in activated and differentiating T cells are under investigation.

We have also demonstrated that activation of Stat3 by IL-6 is inhibited by a novel pathway that acts rapidly and utilizes MAP kinases. The mechanism of inhibition is complex, and likely involves a phosphatase, SHP-2, that inhibits Jak kinase activity. Efforts to identify IL-6 receptor-associated targets for inhibition by MAP kinases, and the targets for dephosphorylation by SHP-2 are ongoing.

**RECENT PUBLICATIONS**


**Sengupta, T. K., Schmitt, E. M. and Ivashkiv, L. B. Inhibition of cytokines and Jak-STAT activation by distinct signaling pathways. Proc. Natl. Acad. Sci. USA 93:9499-9504, 1996.**

**Castro, A., Ruiz D. C. and Ivashkiv, L. B. IL-4 selectively inhibits IL-2-triggered activation of Stat5, but not proliferation, in human T cells. Submitted.**


*Immunology*

# Maria Jasin, Ph.D.

## GENOME DYNAMICS: GENE TARGETING, RECOMBINATION, AND DNA INSTABILITY

One of the most far-reaching developments in biology has been the application of gene targeting to mammalian systems. Gene targeting is the precise alteration of genes within the genome of cells. To achieve this, gene fragments are modified *in vitro* using standard recombinant DNA techniques and reintroduced into cells. The cellular machinery will replace the existing chromosomal copy of the gene with the *in vitro* modified version. Although gene targeting is inefficient in mammalian cells, with random integration of DNA occurring much more frequently, it can be detected and is utilized as a powerful method for manipulating complex mammalian genomes.

To understand the process of gene targeting and homologous recombination mechanisms in general, we have developed new systems for recombination analysis in mammalian cells. By expressing the rare-cutting I-SceI endonuclease in cells, we have introduced breaks into chromosomal DNA, demonstrating that DNA breaks are potent inducers of homologous recombination. Correctly targeted cells comprise as many as 1% of transfected cells, an increase in two to three orders of magnitude over spontaneous gene targeting. The ultimate medical advance for genetic diseases would be the application of gene targeting to gene therapy, the correction of a defective gene in patients. The chromosome break approach we have taken may ultimately have profound ramifications for gene therapy.

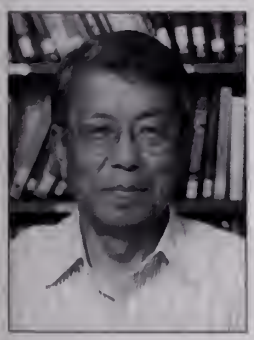
In addition to enhancing gene targeting, the introduction of breaks into the genome allows the study of cellular responses to DNA damage. Recent results in the lab have shown that DNA breaks increase recombination between sister chromatids, homologous chromosomes, and nonhomologous chromosomes. We can predict, therefore, that cellular defects in recombination lead to loss of a major DNA repair pathway, loss of heterozygosity (LOH) at chromosomal loci, and chromosomal translocations. We are currently analyzing the effect of various gene products, including products of the RAD genes and the hereditary breast cancer genes (BRCA1 and BRCA2), in recombination processes and their role on maintaining genomic integrity.

**RECENT PUBLICATIONS**


**Moynahan, M.E. and Jasin, M. Loss of heterozygosity induced by a chromosomal double-strand break. Proc. Natl. Acad. Sci. USA 94:8988-8993, 1997.**

**Liang, F., Han, M., Romanienko, P.J. and Jasin, M. Homology-directed repair is a major double-strand break repair pathway in mammalian cells. Proc. Natl. Acad. Sci. USA, (in press), 1998.**


*Cell Biology & Genetics*



# Tong H. Joh, Ph.D.

## NEUROTRANSMITTER GENE REGULATION AND MECHANISMS OF NEUROPROTECTION

The role of classical neurotranmitters in normal and mental processes and also their dysfunction has been a central theme in neurobiological and behavioral research for many years. The maintenance of the steady state equilibrium of these neurotrasmitters in tissue occurs primarily through regulation of biosynthetic processes. The characterization of genes for neurotransmitter biosynthetic enzymes in our laboratory directs the focus of our efforts toward an understanding of the mechanisms underlying physiological and pharmacological regulation of neurotransmitter biosynthesis at the gene transcription level. Furthermore, the manipulation of these genes allows us to pursue the creation of transgenic mouse models of normal and abnormal gene expression of neurotransmitters and neurotrophins and animal models of human brain diseases, such as Parkinson's disease and abnormal behaviors. The neurotransmitter systems which are currently investigated in our laboratory are dopaminergic, noradrenergic, serotoninergic and nitric oxide systems, and the enzyme include tyrosine hydroxylase, tryptophan hydroxylase, other catecholamine enzymes, GTP cyclohydrolase, a tetrahydrobiopterin cofactor biosynthetic enzyme, and nitric oxide synthase. Our recent finding shows that biopterin cofactor regulation directly affects both monoamine and nitric oxide synthesis, and that proper manipulation of these enzyme genes results in protecting degenerating neurons from apoptosis. Various neuronal degenerating processes, such as neurotrauma, slow degenerating diseases like Parkinson's disease, and aging, are implicated in this study.

**RECENT PUBLICATIONS**


**Tintl, C., Yang, C., Seo, H., Conti, B., Kim, C., Joh, T.H. and Kim, K.S. Structure/function relationship of the cAMP response element in tryosine hydroxylase gene transcription. J. Biol. Chem. 272: 19158-19164, 1997.**

**Hwang, O., Baker, H., Gross, S. and Joh, T.H. Localization of GTP cyclohydrolase in monominergic but not nitric oxide producing cells. Synapse 28: 140-153, 1998.**


*Neuroscience*

# Scott Keeney, Ph.D.

## MEIOTIC RECOMBINATION AND DNA REPAIR

Every sexually reproducing organism, from fungi to humans, uses the specialized cell division pathway of meiosis to generate gametes. During meiosis in most organisms, homologous recombination is absolutely essential for accurate chromosome segregation. From studies in the yeast *Saccharomyces cerevisiae*, it has become clear that recombination results from the induction of a meiosis-specific pathway for the formation and repair of DNA double-strand breaks (DSBs). This highly regulated pathway of self-inflicted DNA damage co-opts and redirects the activities of a number of proteins that also function in recombinational DNA repair in vegetative cells. Many of the components of this pathway are highly conserved evolutionarily, so it is very likely that the detailed molecular mechanisms are also conserved.

We recently showed that the catalytic subunit of the meiotic DNA cleaving activity in yeast is the Spo11 protein. Spo11 cuts DNA through a transesterification reaction, generating a covalent protein-DNA intermediate similar to the one made by DNA topoisomerases. In fact, Spo11 is structurally related to a new family of topoisomerases recently discovered in archaebacteria. We are currently trying to understand in more detail how Spo11 cleaves DNA, and how this cleavage reaction is controlled so that it occurs only at the right time during the cell cycle and at the right places along the chromosomes. To do this, we are characterizing the activities and structure of Spo11 protein and are identifying and characterizing the proteins that interact physically with Spo11. We are also developing systems to study the localization of Spo11 and its associated proteins along meiotic chromosomes inside the cell.

**RECENT PUBLICATIONS**


**Keeney, S. and Kleckner, N. Covalent protein-DNA complexes at the 5' strand termini of meiosis-specific double-strand breaks in yeast. Proc. Natl. Acad. Sci., USA 92:11274-11278, 1995.**

**Keeney, S., Giroux, C.N., and Kleckner, N. Meiosis-specific DNA double-strand breaks are catalyzed by Spo11, a member of a widely conserved protein family. Cell 88:375-384, 1997.**


*Molecular Biology*

# Irwin Klein, M.D.

## HORMONAL AND HEMODYNAMIC REGULATION OF CARDIAC GENE EXPRESSION

Irwin Klein, M.D., Division of Endocrinology, Department of Medicine, North Shore University Hospital and the staff of his laboratory are currently investigating factors which regulate myosin gene expression in heart muscle. Using heart cells in culture, studies are ongoing to understand better how thyroid hormone and hemodynamics, such as heart work and heart rate, are capable of specifically altering gene expression. The heart contains two genetically distinct forms of the heavy chain for the major contractile protein myosin. It has been observed that in hypothyroid hearts, and in human hearts, the predominant form of myosin expressed is the slow or beta myosin. In contrast, in euthyroid animals and in the normally working heart, the fast, alpha myosin, is the predominant gene product. Direct gene transfer studies of the myosin heavy chain promoter indicate that regulation of expression occurs at both the transcriptional level and post transcriptional level. We are currently studying the molecular mechanisms by which the myosin gene promoter responds to changes in cardiac work.

Since heart muscle is a terminally differentiated tissue, it is important to understand the potential transcriptional level regulation which is involved in normal growth and development of this vital organ. It is our purpose to better understand the mechanism by which the heart responds to changing workload and to gain increased insight into the nature of the heart disease which accompanies thyroid dysfunction.

**RECENT PUBLICATIONS**


**Ojamaa, K., Petri, J., Balkman, C., Hong, C. And Klein, I. Post-transcriptional modification of myosin heavy chain gene expression in the hypertrophied rat myocardium. Proc. Natl. Acad. Sci. 91:3468-3472, 1994.**

**Ojamaa, K. Samarel, A., Klein, I. Identification of contractile-responsive element in the cardiac alpha-myosin heavy chain gene. J. Biol. Chem. 270:31276-31281, 1995.**


*Cell Biology & Genetics*

# Andrew Koff, Ph.D.

## CELL CYCLE REGULATION

The goal of this laboratory is to define the mechanism regulating commitment of cells to the mitotic cycle. Commitment occurs during the G1 phase and coincides with a shift of cells from an environmentally dependent state of proliferation to an environmentally independent state. Cyclin-dependent kinases (CDKs) control cell cycle transitions. There are three heterodimeric G1 CDKs, cyclin D/CDK4,6, cyclin E/CDK2, and cyclin A/CDK2. Two families of inhibitory proteins, Inks and Kips, antagonize the activity of CDKs. Our studies focus on the role of the Kip gene family member, p27. The current foci of the laboratory are: 1) p27 interaction with CDKs, 2) regulation of p27 expression, and 3) the role of p27 in development.

To address the first question we are using mutational analysis to clarify how p27 binds to CDKs in a non-inhibitory manner when stoichiometry is low, and how an increase in p27 stoichiometry leads to inhibition. Furthermore, we are trying to understand the differential sensitivity exhibited by the different CDKs to p27-mediated inhibition *in vivo*.

To address the second question, we defined a system where cells withdraw synchronously from the mitotic cycle. Preliminary studies suggest that in this system the amount of p27 increases due to a differential association of p27 mRNA in polysomes. We will continue these studies to determine the mechanism of polysome association.

To address the third question we have created mice lacking the cyclin-dependent kinase inhibitor function of p27. Enhanced growth of mice occurs due to an increase in the number of cycling cells before maturation, and not to increased activity of growth hormone or IGF-I. Our data suggest that cells lacking p27 do not appropriately respond to environmental signals. These animals provide a unique reagent for further studying cell cycle regulation.

**RECENT PUBLICATIONS**


**Millard, S., Yan, J. S., Nguyen, H., Pagano, M., Kiyokawa, H., and Koff, A. Enhanced ribosomal association of $p27^{Kip1}$ mRNA is a mechanism contributing to accumulation during growth arrest. J. Biol. Chem. 11:7093-7098, 1997.**

**Casaccia-Bonnefil, P., Tikoo, R., Kiyokawa, H., Friedrich, V., Chao, M., and Koff, A. Oligodendrocyte precursor differentiation is perturbed in the absence of the cyclin-dependent kinase inhibitor $p27^{Kip1}$. Genes & Devel. 11:2335-2346, 1997.**


*Molecular Biology*

# Richard N. Kolesnick, M.D.

## SIGNAL TRANSDUCTION

The Laboratory of Signal Transduction has had a principal role in the discovery of the Sphingomyelin Signal Transduction Pathway. This is a ubiquitous, evolutionary conserved signaling system analogous to more well-defined systems such as the cAMP and phosphoinositide pathway. The sphingomyelin pathway is initiated by hydrolysis of sphingomyelin to generate ceramide in the plasma membrane by the action of either a neutral or acidic sphingomyelinase. A number of direct targets for ceramide action have now been identified including a ceramide-activated protein kinase (CAPK), a ceramide-activated protein phosphatase, and the protein kinase C isoform zeta. Evidence suggests that the sphingomyelin pathway is a primary signaling pathway linking the 55 kD TNF, Fas, 80 kD interleukin-1 and the 75 kD nerve growth factor receptors to cellular activation. The most comprehensive data have been published for TNFα. Ceramide appears to be a primary mediator of both the inflammatory and apoptotic responses to TNF. With respect to the inflammatory response, ceramide stimulates CAPK to phosphorylate and activate Raf1, which initiates signaling through the MAP kinase cascade, resulting in activation of phospholipase A2 and arachidonic acid release. With regards to apoptosis, TNF induces rapid sphingomyelin hydrolysis to ceramide in virtually all cells in which it initiates apoptosis, and analogs of ceramide but not other lipid second messengers mimic this effect. Recent studies provide strong evidence that ceramide also signals apoptosis for Fas. Ceramide-mediated apoptosis extends beyond cytokine receptors. In collaboration with Zvi Fuks at MSKCC, we showed that ionizing radiation targets membrane, initiating an interphase form of apoptotic cell death that is mediated through the Sphingomyelin Pathway. Further, the chemotherapeutic drug daunorubicin appears to initiate apoptosis by a novel mechanism involving ceramide synthesis via activation of the enzyme ceramide synthase. Ceramide synthesis appears obligatory, since fumonisin B1, a natural specific inhibitor of ceramide synthase, blocked daunorubicin-induced ceramide synthesis and apoptosis. In sum, these studies suggest that ceramide acts as a generic signal for several forms of apoptosis. Ceramide appears capable of initiating apoptosis via a transcriptionally dependent pathway in which stress-activated Protein Kinase/c-Jun Kinase signal up regulation of pro-apoptotic proteins such as Fas ligand, TNF receptor and TRAIL, and by a transcriptionally independent pathway inhibited by Bcl-2 involving mitochondrial dysfunction. These distinct response systems to ceramide elevation are activated in a cell-type specific fashion and may work coordinately.

**RECENT PUBLICATIONS**


**Verheij, M., Bose, R., Lin, X-H., Yao, B., Jarvis, W.D., Grant, S., Birrer, M.J., Szabo, E., Zon, L.I., Kyriakis, J.M., Haimovitz-Friedman, A., Fuks, Z., and Kolesnick, R.N. Requirement for ceramide-initiated SAPK/JNK signalling in stress-induced apoptosis. Nature 378:307-310, 1996.**

**Zhang, Y., Yao, B., Delikat, S., Bayoumy, S., Lin, X-H., Basu, S., Chan-Hui, P-Y., Lichenstein, H., and Kolesnick, R. Kinase suppressor of Ras is ceramide-activated protein kinase. Cell 89:83-92, 1997.**


*Pharmacology*

*Biochemistry & Structural Biology*

# Jason A. Koutcher, M.D., Ph.D.

## *IN VIVO* NUCLEAR MAGNETIC RESONANCE RESEARCH LABORATORY

The *In Vivo* NMR Research Laboratory's focus is on the applications of NMR spectroscopy and imaging to study tumors to 1) determine tumor sensitivity to anti-neoplastic therapy, or 2) to enhance treatment efficacy by optimizing the choice or timing of therapy based on changes in tumor metabolism (biochemical modulation). These studies are performed in animal tumor models (mice), cell culture systems, and in patients. Most recently, we have been working with drugs that inhibit multiple pathways including glycolysis, pentose phosphate pathway, and synthesis of purines and pyrimidines. We have shown that one of these drugs, 6-aminonicotinamide, is a potent radiation sensitizer, both *in vitro* and *in vivo*. Studies on this drug, in combination with other metabolic inhibitors are continuing and appear promising, including cure of a murine tumor model that has not been curable in previous studies These studies involve using multinuclear NMR to monitor tumor metabolism, and these studies determine the time for irradiation. Treatment efficacy is evaluated by measuring tumor growth delay (*in vivo*) or cell plating studies. We also study patients who are being treated to determine whether NMR spectroscopy can non-invasively predict tumor response (prior to tumor shrinkage) and sensitivity to treatment.

In addition, we use high spatial resolution NMR imaging for monitoring changes in tumor volume and anatomy, particularly in the brain. More recently 1H volume localized spectroscopy is being implemented for use in patients to study changes in brain tumor chemistry that occur with treatment.

**RECENT PUBLICATIONS**


**Street, J.C., Mahmood, U., Ballon, D., Alfieri, A., and Koutcher, J.A. 13C and 31P NMR Investigation of effect of 6-Aminonicotinamide on metabolism of RIF-1 tumour cells in vitro. J. of Biol. Chem. 271:4113-4119, 1996.**

**Street, J.C., Alfieri A.A,. and Koutcher, J.A. Quantitation of metabolic and radiobiological effects of 6-Aminonicotinamide in RIF-1 tumor cells in vitro. Cancer Res. 57: 3956-3962, 1997.**


*Physiology, Biophysics & Molecular Medicine*

# Elizabeth Lacy, Ph.D.

## MOLECULAR GENETICS OF MAMMALIAN DEVELOPMENT

We are interested in the molecular and cellular mechanisms that mediate mouse gastrulation, a fundamental developmental process that coordinates complex cell movements with cell proliferation to reorganize and differentiate the embryonic ectoderm into the three definitive germ layers of the fetus: ectoderm, mesoderm, and endoderm. The defining structure of the gastrulating mouse embryo is the primitive streak. Based on fate mapping experiments, the primitive streak can be divided into three functional domains: the proximal region, which gives rise to the extraembryonic mesoderm of the yolk sac; the distal region, which generates definitive endoderm and node derived mesoderm; and the middle streak, which produces lateral plate (kidney, limb) and paraxial (somitic) mesoderm. Currently little is known in the mouse about the mechanisms that mediate the assembly of the primitive streak into these functional domains or about the signaling pathways that specify the different types of mesoderm generated from the streak. To gain insight into the process of gastrulation, we are studying *amnionless (amn)*, a recessive transgene induced mouse mutation that specifically impairs the formation and/or specification of the middle streak. Our analyses of the *amn* mutant have revealed that middle streak assembly is mediated by a previously unknown pathway, one that is genetically separable from those directing the formation of the proximal and distal streak regions. Therefore, a disrupted gene at the *amn* locus must play a key role in this pathway. Additionally, chimera analyses have shown that this gene, the *amn* gene, functions in the visceral endoderm to direct the formation of the middle streak by the overlying embryonic ectoderm. Ongoing research in the laboratory is concentrating on cloning the *amn* gene through BAC/YAC contig building and BAC/YAC transgene rescue experiments. These studies will set the stage for future research on the genetic pathway for middle streak formation and on the role of the visceral endoderm in patterning the embryonic ectoderm during gastrulation.

**RECENT PUBLICATIONS**


**Wang, X., Bornslaeger, E., Haub, O., Newberger, C.L., Lonberg, N., Dinulos, M.B., Disteche, C.M., Copeland, N.G., Gilbert, D.J., Jenkins, N.A., and Lacy, E. A candidate gene for the *amnionless* gastrulation stage mouse mutation encodes a TRAF related protein. Devel. Biol. 177:274-290, 1996.**

**Tomihara-Newberger, C., Haub, O., Lee, H.-G., Soares, V., Manova, K., and Lacy, E. The *amn* gene product is required in visceral endoderm for the generation of middle streak derivatives. Submitted 1998.**


*Molecular Biology*

# Eseng Lai, M.D., Ph.D.

## TRANSCRIPTIONAL CONTROL OF MAMMALIAN DEVELOPMENT

The long term goal of my laboratory is to understand the molecular mechanisms controlling development in mammals. Our work focuses on two genes, called BF-1 and BF-2 (brain factors-1 and 2), which are members of the winged-helix family of transcription factors. We determined the function of BF-1 and BF-2 in mouse development by generating animals with a targeted disruption of these genes. Mice lacking BF-1 have severe abnormalities in the development of the cerebral hemispheres. Although the telencephalic vesicles are formed, they fail to grow normally. In the absence of BF-1, the telencephalic progenitors prematurely withdraw from the cell cycle. This results in the early depletion of the population of neuronal progenitors, and ultimately results in fewer neurons in the cerebral hemispheres. Using cell culture models, we have demonstrated that BF-1 enhances G1 to S progression and can antagonize the activity of TGF-β. BF-1 blocks the induction by TGF-b of the cdk inhibitor, p15. Surprisingly, these activities of BF-1 do not require its DNA binding activity, raising the possibility that BF-1 may interact directly with components of the TGF-β signalling pathway. The disruption of BF-2 leads to severe anomalies in kidney development. BF-2 expression is restricted to the stromal mesenchyme of the embryonic kidney. Loss of the BF-2 mutant leads to abnormal differentiation of two other components of the embryonic kidney, the nephrogenic mesenchyme and ureteric bud epithelium. Our findings demonstrate that BF-2 is required for the ability of the stromal mesenchyme to promote normal kidney development. We are currently investigating the hypotheses that 1) BF-1 regulates the response of neuronal progenitors to the activity of TGF-β superfamily members such as the bone morphogenetic proteins (BMPs) during brain development, and 2) BF-2 may regulate the production of extracellular signals by the stromal mesenchyme.

**RECENT PUBLICATIONS**


**Hatini, V., Huh, S., Herzlinger, D., Soares, V.C. and Lai, E. Essential role of stromal mesenchyme in kidney morphogenesis revealed by targeted disruption of Winged-Helix transcription factor, BF-2. Genes & Dev. 10:1467-1478,1996.**

**Dou, C., Ye, X., Stewart, C., Lai, E. and Li, S.C. TWH regulates the development of spinal cord neurons. Neuron 18:539-551, 1997.**


*Cell Biology & Genetics*

*Neuroscience*

# Harry M. Lander, Ph.D.

## REDOX-MEDIATED SIGNAL TRANSDUCTION

Free radicals such as nitric oxide and hydroxyl radical play important physiological and pathophysiological roles. The focus of research in our laboratory is to define the mechanisms and pathways by which reactive free radicals transmit signals to the nucleus. We approach this problem at the biochemical and molecular level. Immune cells appear to have a preset program of signal transduction upon alteration of their redox status. We are actively piecing together the transductional mechanisms by which reactive nitrogen, such as nitric oxide, and other free radicals initiate gene transcription. Our recent work has identified guanine nucleotide-binding proteins (G proteins), in particular $p21^{ras}$, as targets of free radicals. Furthermore, we are identifying the effectors and dowstream molecules, such as intermediary kinases and phosphatases, which propagate free radical signals between the cell membrane and the nucleus.

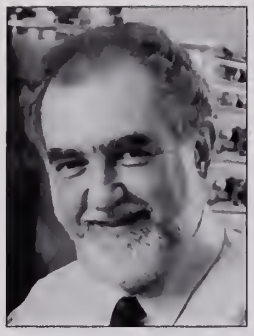
We are also defining the structural alterations initiated by nitric oxide and other free radicals on their target proteins. Using both site-directed mutagenesis and electrospray-ionization mass spectrometry, we are begining to understand the exact molecular alteration responsible for redox-activation of G proteins, and we are gaining insight into the conformational consequences of free radical signaling. For example, we have defined a single Cys residue in $p21^{ras}$ which is modified by nitric oxide and triggers activation. Future studies include: 1) understanding how nitrosothiol formation, the result of a nitric oxide-Cys interaction alters protein function; 2) defining novel protein-protein interactions induced by reactive free radicals, and 3) cloning and characterizing these proteins as a means of defining novel signal transduction pathways. Using these structural and molecular techniques, we anticipate gaining greater knowledge of how cells respond to alterations in redox state.

**RECENT PUBLICATIONS**


**Lander, H. M. An essential role for free radicals and related species in signal transduction. FASEB Journal 11:118-124, 1997.**

**Lander, H. M., Ogiste, J. S., Tauras, J. M., Hori, O., Moss, R. A., and Schmidt, A.-M. Activation of the receptor for advanced glycation end products triggers a $p21^{ras}$-dependent MAP kinase pathway regulated by oxidant stress. J. of Biol. Chem. 272:17810-17814, 1997.**


*Biochemistry & Structural Biology*



# Roberto Levi, M.D.

## CARDIOVASCULAR PHARMACOLOGY

Histamine (HA) is released immunologically or by ischemia-reperfusion (I/R) from cardiac mast cells (MC), causing severe $H_2$-receptor(H2R)-mediated tachyarrhythmias. Cardiac MC have been recently demonstrated to intensely proliferate in ischemic cardiomyopathies, via the release of stem factor. These MC are close to sympathetic nerve terminals (SNT), which we have discovered to contain a different HA receptor subtype, $H_3R$, that inhibits norepinephrine (NE) release. $H_3R$ are normally quiescent, yet fully activated in hyperadrenergic states, such as myocardial ischemia, when HA is copiously released. We are now testing whether $H_3R$ are also activated in the failing heart. Further, we study the transductional mechanisms associated with $H_3R$-mediated inhibition of NE release in normal and ischemic SNT (synaptosomes) isolated from guinea pig hearts, from dogs in cardiac failure and from surgical specimens of human right atrium. Our postulate is that $H_3R$ attenuate NE exocytosis (associated with acute ischemia) and "carrier-mediated" release (associated with protracted ischemia and Na+/H+ antiporter activation), by inhibiting PI turnover and PKC activity. Negative modulation of NE release is cardioprotective, because it decreases the incidence and severity of arrhythmias and attenuates coronary vasoconstriction. Among other putative endogenous modulators of cardiac sympathetic neurotransmission, we are assessing in cardiac synaptosomes the effects of bradykinin (BK), which we find to enhance NE exocytosis as a function of its concentration. We have recently discovered that SNT themselves produce enough BK to modulate adrenergic transmission positively in the heart by an autocrine action on SNT. Further, BK acts by a paracrine action on sensory C-fiber endings to evoke the release of neuropeptides mediators (eg, CGRP) that subsequently act on adrenergic nerve endings to promote NE release. Thus, we have uncovered a very important crosstalk between adrenergic and C-fiber endings that serves as an amplification system in pathophysiological states such as myocardial ischemia. The ultimate goal of our research is to generate novel and significant information towards the development of new therapeutic strategies in cardiovascular diseases.

**RECENT PUBLICATIONS**


**Hatta, E., Yasuda, K. and Levi, R. Activation of histamine $H_3$-receptors inhibits carrier-mediated norepinephrine release in a human model of protracted myocardial ischemia. J. Pharmacol. Exp. Ther. 283:494-500, 1997.**

**Seyedi, N., Win, T., Lander, H.M. and Levi, R. Bradykinin $B_2$-receptor activation augments norepinephrine exocytosis from cardiac sympathetic nerve endings: mediation by autocrine/paracrine mechanisms. Circ. Res. 81:774-784, 1997.**


*Pharmacology*

# Lonny R. Levin, Ph.D.

## MOLECULAR GENETIC ANALYSIS OF ADENYLYL CYCLASE FUNCTION

Mammals possess two distinct classes of adenylyl cyclase (AC), the effector molecule of the cAMP signaling pathway. One class resides in the plasma membrane and transduces extracellular signals into intracellular changes; the second is a recently isolated, cytosolic enzyme of unknown function. The first class, the hormone-responsive ACs, consists of a family of structurally related, transmembrane isoforms (tmACs) possessing distinct regulatory mechanisms and tissue distributions. These tmACs are modulated by heterotrimeric G proteins as well as molecules from other second messenger systems. This diversity of regulatory properties enables tmACs to integrate various signals into coordinated cAMP responses and resultant physiological effects dependent upon the particular AC isoform expressed.

The only known role of a specific mammalian tmAC isoform was first determined by molecular genetic studies on its Drosophila melanogaster homolog. The gene encoding Drosophila AC1 is required for proper learning and memory in the fly. Gene knockout experiments in mouse confirmed a similar role for mammalian AC1, indicating function is conserved between flies and mammals. To determine the specific biological role of other tmACs, we have identified and cloned a number of Drosophila tmACs, related them to known mammalian isoforms, and begun using molecular genetic techniques to determine their individual physiological functions.

In collaboration with Dr. Jochen Buck's Laboratory, we have recently isolated the gene encoding a soluble form of AC (sAC) from mammals. Although sAC activity was first detected over 20 years ago, nothing is known of its function or mechanism of regulation. In fact, by isolating its gene, we provided the first, unequivocal evidence that sAC activity is not derived from proteolytic degradation of a tmAC. We are currently investigating the tissue distribution and subcellular localization of sAC protein and its mode of enzymatic regulation. Additionally, we are determining its physiological function by creating mice deficient for the sAC gene product.

**RECENT PUBLICATIONS**


**Iourgenko, V., Kliot, B., Cann, M.J., and Levin, L.R. Cloning and characterization of a Drosophila adenylyl cyclase homologous to mammalian type IX. FEBS Let. 413:104-108, 1997.**

**Cann, M.J. and Levin, L.R. Genetic characterization of adenylyl cyclase function. In Advances in Second Messenger and Phosphoprotein Research: Adenylyl Cyclases. D.M.F. Cooper, ed. (New York: Raven Press), pp 121-135, 1998.**


*Pharmacology*

*Neuroscience*

# Gloria C. Li, Ph.D.

## STRESS RESPONSE AND KU AUTOANTIGEN

Our current research focuses on the elucidation of molecular control mechanisms of cellular response to stress, including heat shock and ionizing radiation. We are testing a hypothesis inferred from our earlier studies that there is a dual control mechanism in the heat shock response: a positive control mediated via the heat shock transcription factor HSF1, and a negative control mediated via the Ku autoantigen. Ku autoantigen is a DNA-binding protein consisting of 70-kDa (Ku70) and 86-kDa (Ku80) subunits. By virtue of its DNA-binding activity, Ku serves as a regulatory component of the mammalian DNA-dependent protein kinase, DNA-PK. Recent data have implicated Ku/DNA-PK complex in the repair of DNA double-strand breaks (DSB) and V(D)J recombination.

To investigate that Ku may play a role in the regulation of heat shock response, we have established rodent cell lines that stably and constitutively overexpress one or both Ku subunits. We have shown that overexpression of Ku70, but not Ku80, specifically suppresses heat-induction of hsp70. Thermal induction of the other heat shock proteins is not affected, nor is the activation of HSF1. These findings strongly suggest that mammalian Ku-protein is involved in the regulation of hsp70 gene expression.

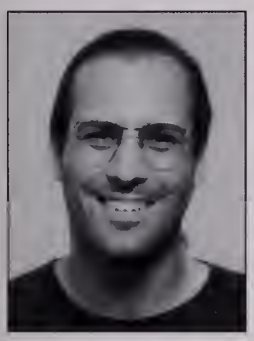
To understand further the mechanistic and functional aspects of Ku protein in modulating cellular response to stress, specifically its roles in transcription and DNA repair, we have initiated studies to establish homozygous cell lines in which both alleles of Ku are inactivated through gene-targeting mutagenesis. We have obtained Ku80-/- and Ku70-/- cell lines, and generated Ku80-/- and Ku70-/- homozygote mutant mice. These Ku80-/- and Ku70-/- cell lines, their derivatives expressing various mutant Ku subunits, and the Ku-deficient mice can be used directly in the analysis of the potential roles of Ku in transcriptional regulation, in x-ray sensitivity, and in recombination.

**RECENT PUBLICATIONS**


**Nussenzweig, A,. Chen, C., da Costa Soares, V., Sanchez, M., Sokol, K., Nussenzweig, M.C., and Li, G.C. Requirement for Ku80 in growth and V(D)J recombination. Nature 382:551-555, 1996.**

**Ouyang, H., Nussenzweig, A., Kurimasa, A., da Costa Soares, V., Li, X., Cordon-Cardo, C., Li, W., Cheong, N., Nussenzweig, M., Iliakis, G., Chen, D.J., Li, G.C. Ku70 is required for DNA Repair but not for TCR Gene Recombination in vivo. J Exp Med. 186:921-929, 1997.**


*Physiology, Biophysics & Molecular Medicine*



# Christopher D. Lima, Ph.D.

## STRUCTURE/FUNCTION ANALYSIS OF NOVEL HUMAN PHOSPHOTRANSFERASE ACTIVITIES

The primary goal of our current research is to understand, at the atomic level, the basis for protein phosphotransferase activity in human biology.

Our main areas of interest involve: (1) specific protein phosphotransferase/hydrolase activity, and (2) how this may play a role in human carcinogenesis and metabolism. We primarily utilize X-ray crystallography to decipher specific mechanisms in these systems, however, we are also developing and utilizing cell-based, genetic and biochemical assays to elucidate structure/function relationships. We are currently developing several systems to elucidate structure/function relationships for the HIT (histidine triad) protein family. This protein family is highly conserved and found throughout all known life forms with the exception of viruses. It is likely that members of this protein family catalyze a conserved nucleotidylyl transferase activity, although divergent family members exist which may play other vital roles in the cell. We have determined the crystal structures of three members of this family, two from human, one of which has been putatively identified as a novel human tumor suppressor, and one from bacteria. These structures have helped elucidate the catalytic mechanism for the HIT protein family and have also provided insight into the level of conservation between divergent human family members and their bacterial counterparts. We are pursuing the structure solution of several other divergent members of this class of enzymes, as well as developing genetic and biochemical assays to elucidate the *in vivo* role for this conserved protein family. We are utilizing mutational analysis of many members of this family so that we can more fully understand their mode of action. The comprehensive approach we have outlined will likely provide the insights necessary to uncover the functional roles for this protein family in human biology and its pertinent role in human carcinogenesis.

We are currently expanding our studies to include that of yet another novel human protein implicated in cancer which catalyses a phosphotransferase/hydrolase reaction, something we hope to elucidate further with our structural and biochemical approach. We make extensive use of X-ray methods which include an emphasis on synchrotron radiation and multiwavelength anomalous diffraction phase determination, a powerful method for 'solving' a protein's structure.

**RECENT PUBLICATIONS**


**Lima, C.D., Rosenbaum, G., D'Amico, K., Westbrook, E.M., Hendrickson, W.A. MAD analysis of FHIT, a putative human tumor suppressor from the HIT protein family. Structure 5: 763-774, 1997.**

**Lima, C.D., Klein, M.D., Hendrickson, W.A. Structure-based anaylsis of catalysis and substrate definition in the HIT protein family. Science 278: 286-290, 1997.**


*Biochemistry & Structural Biology*

# C. Clifton Ling, Ph.D.

## ONCOGENES IN RADIATION-INDUCED EFFECTS

The oncogenes ras and myc have diverse biological significance. They are cooperating oncogenes that transform primary cells, affect cells' response to radiation, and modulate apoptosis. Our lab has been broadly interested in the study of these oncogenes, relative to radiation-induced biological effects. We exploited their role in cancer development for the investigation of radiation-induced carcinogenesis, and have linked a point-mutation in N-ras to the radiation-induced transformed phenotype. The influence of ras and myc oncogenes on radioresistance has been documented and the possible involvement of signal transduction pathways and of DNA repair have been investigated. Our current studies concern the modulation of radiation-induced apoptosis by myc and ras expression.

**RECENT PUBLICATIONS**


**Sahoo, N, Ling CC, Anderson LL. Analysis of factors affecting the therapeutic gain in high dose rate gynocological implants relative to low dose rate implants. Medical Physics 23: 419-425, 1996.**

**Ling CC, Burman C, Chen CS, Kutcher GJ, Leibel, SA, LoSasso, T, Mohan R, Bortfeld T, Reinstein L, Sirou S, Wang, XH, Wu Q, Zelefsky M, Fuks Z. Conformal radiation treatment of prostate cancer using inversely-planned intensity-modulated photon beams produced with dynamic multileaf collimation. Int. J. Radiation Oncology Biol. Phys. 35: 721-730, 1996.**


*Physiology, Biophysics & Molecular Medicine*

# Hsiou-Chi Liou, Ph.D.

## MOLECULAR IMMUNOLOGY OF LYMPHOCYTE DIFFERENTIATION AND APOPTOSIS

The primary objective of our research is to understand gene regulation and signal transduction events that control differentiation, proliferation, and apoptosis in lymphocytes. We have been focusing on the key transcription factors and signaling molecules in these processes, and are interested in investigating how the deregulation of these molecules may lead to immunodeficiency or tumorigenesis of the immune system. Specific projects include:

***The role of NF-c-Rel in immune regulation***

c-Rel is a lymphoid-specific member of the NF-/Rel transcription factor family that is important for immune regulation. My laboratory has generated the c-Rel knockout mouse and shown that lymphocytes derived from the c-Rel(–/–) mice have impaired proliferative response as well as reduced cell viability. Several research projects are in progress in my laboratory which take advantage of the unique c-Rel knockout mouse model. These projects are intended: (1) To study how c-Rel is involved in cell cycle control; (2) To identify the c-Rel target genes; (3) To investigate the role of c-Rel in cell survival and B cell tolerance; and (4) To explore the function of c-Rel in Ig isotype switching.

***Apoptotic signaling pathways***

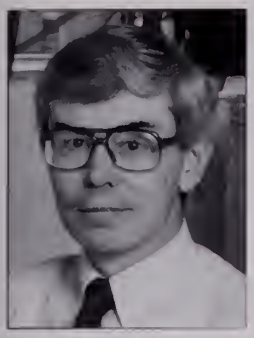
IgM and the TNF superfamily molecules (e.g. Fas, CD40, TNF) play critical roles in the cellular decision between proliferation and apoptosis. To investigate the apoptosis mechanism, we cloned several novel proteins that are associated with the TNF receptor (p60) using the yeast two-hybrid screening method. The following approaches will be taken to dissect the apoptotic and survival signaling events: (1) To investigate the apoptotic mechanism mediated by the Death domain associated proteins (DAPs); (2) To investigate the role of NF-/Rel and other signaling molecules in CD40 mediated cell viability; and (3) To explore how the antigen receptor triggers the ICE-caspase pathways.

**RECENT PUBLICATIONS**


**Andjelic, S., and Liou, H.-C. Activation-induced B lymphocyte apoptosis is mediated via a protease from the caspase family. Eur. J. Immunol. 28:570-581, 1998.**

**Tumang, J., Owyang, A., Andjelic, S., Jin, Z., Hardy, R.R., Liou, M.-L. and Liou, H.-C. C-Rel is Essential for B Lymphocyte Survival, Cell Cycle Progression, and Terminal Differentiation. Eur. J. Immunol. 28, 1-14, 1998.**


*Immunology*



# Kenneth O. Lloyd, Ph.D.

## TUMOR ANTIGEN IMMUNOCHEMISTRY

The overall aim of this laboratory is to detect, analyze, and characterize cell-surface antigens of human tumor cells, with special emphasis on carbohydrate determinants. The goal is to recognize antigens that are either restricted to tumor cells or show a preferential expression on such cells. Glycoproteins and glycolipids are prominent constituents of the surface of all mammalian cells. Carbohydrate moieties of these components play important roles in cell-cell interactions, as receptors for various ligands, and in development and differentiation. Many of the most important tumor antigens detected using mouse and human monoclonal antibodies carry carbohydrate epitopes.

Gangliosides (sialylated glycosphingolipids) are particularly important antigens in tumors of neuroectodermal origin (melanoma, neuroblastoma, and astrocytoma). Our laboratory has characterized a number of mouse and human monoclonal antibodies that recognize gangliosides, and has determined the expression and biosynthesis of glycolipids in various tumor types. In addition to being carried on lipid moieties, many carbohydrate determinants are found on protein backbones. Mucins are a class of highly glycosylated glycoproteins that carry many important antigenic structures, particularly in epithelial cells. Notable among these are the blood specificities of the A,B,H Lewis family. Using a panel of well-characterized antibodies, we are analyzing the altered expression of blood group antigens in epithelial cancers. A number of mucins, in particular CA-125 (an important ovarian cancer antigen), are being studied in detail.

Newer areas of investigation include an effort to develop carbohydrate-based vaccines for the treatment of cancer. In these studies, various carbohydrate (e.g. Ley)-protein conjugates are synthesized and characterized and their immunogenicity is tested in mouse models. In collaboration with Memorial Hospital colleagues the most immunogenic constructs are then studied in Phase 1 and Phase 2 clinical trials.

**RECENT PUBLICATIONS**


**Lloyd, K. O., Burchell, J., Kudrashov, V., Yin, B.W.T., and Taylor-Papadimitriou J. Comparison of O-linked carbohydrate chains in MUC-1 mucin form breast epithelial cell lines and breast carcinoma cell lines. J. Biol. Chem. 271: 33325-33334, 1996.**

**Kudrashov, V., Kim, H., Ragupathi, M., Danishefsky, S. J., Livingston, P. O. and Lloyd, K. O. Immunogenicity of synthetic conjugates of Lewisy oligosaccharide with protein in mice: towards the design of anti-cancer vaccines. Cancer Immunol. Immunother. 45: 281-286, 1998.**


*Immunology*

# Min Lu, Ph.D.

## MECHANISMS OF VIRAL MEMBRANE FUSION

We are using a combination of biophysical, structural, and biochemical approaches to study the three-dimensional structure and biological function of the HIV-1 envelope glycoprotein that mediates fusion of viral and cellular membranes. We hope to establish the biophysical and structural basis of the conformational changes in the gp120/gp41 complex that are required for activation of membrane fusion.

Our long-term goal is to gain a detailed understanding of the structural, biophysical, and biological properties of the HIV-1 glycoprotein complex, and to relate this understanding to its *in vivo* function. This includes defining both the native and fusogenic conformations of gp41, the nature of its conformational change, and the role of gp120 in controlling this structural rearrangement, as well as characterizing the functional determinants in both the gp41 core and peptides found to have antiviral activity.

We make use of structural dissection of proteins into modules. This methodology can make it possible to develop and study simple model systems that display the essential features to be examined. Determining structural details of these modules at atomic resolution further allows us to attack fundamental mechanistic questions in biology in greater details than is often possible by starting with larger, more complex systems.

**RECENT PUBLICATIONS**


**Lu, M., and Kim, P. S. A trimeric structural subdomain of the HIV-1 transmembrane glycoprotein. J. Biomol. Struct. Dyn. 15, 465-471, 1997.**

**Tan, K., Liu, J. H., Wang, J. H., Shen, S., and Lu, M. Atomic structure of a thermostable subdomain of HIV-1 gp41. Proc. Natl. Acad. Sci. USA 94, 12303-12308, 1997.**


*Biochemistry & Structural Biology*

# Neal F. Lue, M.D., Ph.D.

## TELOMERE REPLICATION

Telomeres in most organisms are maintained by a specialized reverse transcriptase known as telomerase. A ribonucleoprotein, telomerase uses an integral RNA component as the template for the synthesis of one strand of the telomere terminal repeats. The absence of telomerase in normal somatic cells causes chromosomes to shorten progressively with each cell division, leading eventually to inviability. Activation of telomerase in germ cells and cancer cells, however, results in restoration of telomere length and enables these cells to divide indefinitely. The ability to manipulate telomerase activity may therefore lead to new therapeutic strategies for the treatment of cancer and aging.

Our laboratory studies the mechanisms and regulations of telomerase with the ultimate aim of exploiting the medical potential of this enzyme. We are currently focused on three areas:

(1) We have found that telomerase activity can be inhibited by a tight interaction between the enzyme and an upstream region of the telomeric primer. A combination of biochemical and molecular genetic experiments are underway to define the structural basis for this tight interaction, and the physiologic relevance of this regulation.

(2) We have noticed intriguing parallels between telomerases and a group of mobile genetic elements known as non-LTR retrotransposons. For example, both telomerase and the retrotransposon employ a reverse transcriptase and an endonuclease in carrying out their respective functions. The molecular and evolutionary implications of this similarity are being explored.

(3) We have developed a novel affinity purification technique for telomerase. Large scale preparation of this enzyme is in progress to uncover potential novel subunits of telomerase and determine their functions in chromosome maintenance.

**RECENT PUBLICATIONS**


**Nugent, C.I., Hughes, T.R., Lue, N.F., and Lundblad, V.I. Cdc13p: A single-strand telomeric DNA binding protein with a dual role in yeast telomere maintenance. Science 274:249-252, 1996.**

**Lue, N.F. and Peng, Y. Negative regulation of yeast telomerase activity through an interaction with an upstream region of the DNA primer. Nucl. Acids Res. 26:1487-1494, 1998.**


*Molecular Biology*

# Lucio Luzzatto, M.D.

## HUMAN MOLECULAR GENETICS

Our main common purpose is to elucidate the nature of mutations underlying inherited and acquired human diseases, and the mechanisms whereby mutations produce disease manifestations. Our ultimate aim is to develop new approaches to treating human diseases by gene transfer methods.

We are concentrating particularly on two systems.

(1) *Paroxysmal nocturnal hemoglobinuria (PNH)*. This acquired condition is due to a specific abnormality of the red cell membrane, which makes the red cells excessively prone to lysis by complement. We now know that this is due to somatic mutations in one of the genes (called PIG-A) of the glycan phosphatidylinositol biosynthetic pathway. PNH is related to aplastic anemia (AA), and sometimes PNH evolves to acute leukemia. Thus, PNH is a prototype example of a clonal non-malignant disorder. We intend to investigate the basis for the relative selective advantage which the PNH clone appears to enjoy in a hypoplastic marrow by in vitro culture methods, by creating mouse models of PNH, and by PIG-A knockout in embryonic stem cells or in erythroid cells. What we learn could help us to design stem-cell manipulations useful for the treatment of PNH and possibly of AA.

2. *Glucose 6-phosphate dehydrogenase (G6PD)*. Deficiency of this enzyme is well known to predispose to acute hemolytic attacks following exposure to a variety of exogenous triggers. We have previously cloned the human G6PD gene, identified numerous mutations, characterized its transcriptional control elements, and recently outlined the three-dimensional structure of its enzyme product. Because we found that rare patients have specific mutations causing a severe form of disease (chronic non-spherocytic hemolytic anemia, or CNSHA), we intend to construct a retroviral vector able to transfer into hematopoietic cells the normal G6PD gene in a form that can be expressed. This approach could benefit patients with CNSHA, and also serve as a model system to explore the self-selection of phenotypically corrected stem cells.

**RECENT PUBLICATIONS**


**Corcoran, C.M., Fraser, P., Martini, G., Luzzatto, L. And Mason, P.J. High-level regulated expression of the human G6PD gene in transgenic mice. Gene 173:241-246, 1996**

**Luzzatto, L., Bessler, M. And Rotoli, B. Somatic muttions in paroxysmal nocturnal hemoglobinuria: a blessing in disguise? Cell 88:1-4, 1997.**


*Cell Biology & Genetics*

# Thomas Maack, M.D.

## HORMONES AND RECEPTORS IN CARDIOVASCULAR AND RENAL FUNCTION

Cardiovascular and renal functions are geared towards the maintenance of the internal environment in the mammalian organism, including the homeostatic regulation of plasma volume and composition, and of blood pressure. Our research has been directed at some of the hormones and receptors involved in these essential homeostatic mechanisms. Particular attention has been devoted in the past decade to the study of atrial natriuretic factor (ANF) and its receptors.

Studies by several laboratories, including our own, revealed that ANF is a 28 amino acid polypeptide hormone secreted by the heart atria when blood volume or pressure increases. ANF leads to an increase in sodium excretion by the kidney, an inhibition of the renin-angiotensinaldosterone system, vasorelaxation, and an increase in capillary permeability that tend to return plasma volume and pressure to normal levels. These effects are mediated by specific receptor (GCA-ANF receptor), which generates cGMP, the major second messenger of ANF actions. A second class of receptors, named by us clearance receptors (C-ANF receptors), is involved in the removal of ANF from plasma by a process of receptor-mediated endocytosis, *In vivo* blockade of C-ANF receptors by small ligands increases plasma levels of ANF, a finding that is of potential therapeutic importance in the treatment of cardiovascular and renal diseases. After having elucidated the overall systemic role and cellular mechanisms of the clearance function of C-ANF receptors, we are presently investigating the molecular mechanisms of this function by using recombinant DNA and mutagenesis techniques, We are also actively investigating the dynamics of ANF interaction with recombinant wild type and mutated GC-A-ANF receptor to determine the molecular mechanisms by which ANF exerts its biological actions. In addition, studies of other members of the family of natriuretic peptides (BNP, CNP) and of angiotensin receptors are subjects of interest to the laboratory.

**RECENT PUBLICATIONS**


**Cohen, D., Koh, G.Y., Nikonova, L.N., Porter, J.G., and T. Maack. Molecular determinants of the clearance function of type C receptors of natriuretic peptides. J. Biol. Chem. 271: 9863-9869, 1996**

**Maack, T. Role of atrial natriuretic factor in volume control. Kidney Internat. 49: 1732-1737, 1996.**


*Physiolgoy, Biophysics & Molecular Medicine*

# Kenneth J. Marians, Ph.D.

## NUCLEIC ACIDS BIOSYNTHESIS

Our work focuses on: i) how the proteins at the replication fork cooperate to coordinate coupled leading- and lagging-strand synthesis, ii) the mechanism of initiation of recombination-dependent DNA replication, and iii) the mechanism of action of topoisomerases and their interaction with the replication and partition apparatuses.

Current studies on replication fork action are focused on: i) how the protein-protein interaction between the tau subunit of the DNA polymerase III holoenzyme—the replicative polymerase—and DnaB—the replication fork helicase, which is required for proper replisome function, is accommodated between components that rotate in space with respect to one another, and ii) defining the temporal sequence of enzymatic events and required protein-protein interactions during the lagging-strand cycle and identifying the signal for primer synthesis.

We have reconstituted primosome-dependent replication fork assembly at D-loops, the initiating structure for homologous recombination. We are currently investigating alternative paths of fork assembly and the influence of the recombination proteins in this process. We have also identified four D-loop binding proteins from human cells and are in the process of characterizing them.

We have identified genetically an interaction between topoisomerase IV, the enzyme responsible for decatenating the daughter chromosomes, and the gamma subunit of the holoenzyme. Although the biochemical basis of this interaction is not yet clear, it has raised the exciting possibility of the existence of a signal transaction pathway linking termination of DNA replication and chromosome segregation.

Our studies on topoisomerase mechanism has shown that double-strand break formation, the cytotoxic event resulting from treating either bacteria or human cells with a type II topoisomerase inhibitor, is a two-step process. First, a collision between a replication fork and a topoisomerase-drug-DNA ternary complex freezes the topoisomerase, then a double strand break is created by the action of other, presumably repair, enzymes in the cell. We are currently purifying the enzymes responsible for formation of the double-strand break.

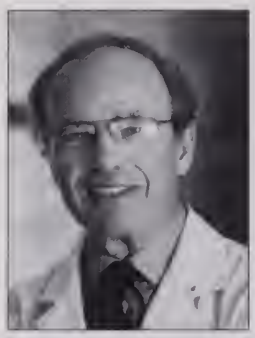
**RECENT PUBLICATIONS**


**Marians, K.J., Hiasa, H., Kim, D.R., and McHenry, C.S. Role of the core DNA polymerase III subunits at the replication fork. Alpha is the only subunit required for processive replication. J. Biol. Chem. 273:2452-2457, 1998.**

**Levine, C. and Marians, K.J. Identification of *dnaX* as a high-copy suppressor of the conditional lethal and partition phenotypes of the *parE10* allele. J. Bacteriol. 180:1232-1249, 1998.**


*Biochemistry & Structural Biology*

*Molecular Biology*



# Paul A. Marks, M.D.

## DEVELOPMENTAL CELL BIOLOGY

The research goals of this laboratory are to explore the cellular and molecular mechanisms involved in the induction of differentiation of transformed cells and to design and develop novel differentiation-inducing agents with potential for clinically effective chemotherapy and chemopreventives for cancer. Cancer cells, although transformed by virtue of the action of a complex and essentially irreversible patterns of inherited and acquired gene mutations, still retain, at least in many instances, the capacity to express a normal or almost normal pattern of cellular differentiation characteristic of the parent cell lineage of the cancer. This pattern may include the reestablishment of normal terminal cell division and the loss of suppression of the malignant oncogenic properties of the cancer cells. As an experimental model, the laboratory studies the virus-transformed murine erythroleukemia cell (MELC), and several transformed cell lines derived from human tumors. We have demonstrated that culture with any of a number of chemical agents of the family of hybrid polar compounds, of which hexamethylene bisacetamide (HMBA) is the prototype, is capable of inducing terminal differentiation or apoptosis developmental patterns in a wide variety of transformed cells, *in vitro*. The potential of hybrid polar compounds in the prevention and treatment of cancers are being investigated in animal models. In PhaseI/II clinical trials with HMBA, it was demonstrated that these agents can induce differentiation of transformed cells in patients with myelodysplastic syndrome and acute myelogenous leukemia.

Current studies are directed toward elucidating the mechanism of action of highly potent second generation hybrid polar compounds.

**RECENT PUBLICATIONS**


**Richon, V.M., Emiliani, S., Verdin, E., Webb, Y., Breslow, R., Rifkind, R.A. and Marks, P.A. A class of hybrid polar inducers of transformed cell differentiation inhibits histone deacetylases. Proc. Natl. Acad. Sci. USA 95:3003-3007, 1998.**

**Siegel, D.S., Zhang, Z.X., Feinman, R., Teitz, T., Zelenetz, A., Richon, V.M., Rifkind, R.A., Marks, P.A. and Michaeli, J. Hexamethylene bisacetamide induces programmed cell death (apoptosis) and down-regulates BCL-2 expression in human myeloma cells. Proc. Natl. Acad. Sci. USA 95:162-166, 1998.**


*Cell Biology & Genetics*

# Joan Massagué, Ph.D.

## THE TGF-β SIGNALING NETWORK OF CELL CONTROL

This laboratory is elucidating the mechanisms that mediate the growth inhibitory and developmental effects of transforming growth factor β (TGF-β) and related polypeptide growth factors. The TGF-β family regulates cell division, differentiation, motility, adhesion, and death in virtually all tissues and organisms from fruitfly to human. Signal transduction by these factors involves three classes of molecules: a family of membrane receptor serine/threonine kinases, a family of cytoplasmic proteins—the Smad family—that serves as substrates for these receptors, and nuclear DNA-binding factors that associate with Smads forming transcriptional complexes. Signaling is initiated by binding of the growth factor to a specific pair of receptor kinases, an event that induces the phosphorylation and activation of one kinase by the other. The activated type I receptor phosphorylates a subset of Smads or R-Smads which then move into the nucleus. On their way to the nucleus, R-Smads associate with the related protein Smad, a tumor suppressor gene product. In the nucleus, this complex may associate with specific DNA-binding proteins that direct it to the regulatory region of target genes. TGF-β signals generated and conveyed in this fashion cause growth arrest by controlling the activity of cyclin-dependent kinases that propel cells through the G1 phase of the cell cycle. The integrity of the TGF-β signaling network is essential for normal development and tissue homeostasis, and its disruption by mutation underlies several human inherited disorders and cancer. Current research in this laboratory is focusing on the identification of determinants of specificity in this signaling network, the structural and functional analysis of Smad transcriptional complexes, the identification of regulatory crosstalk between this and other pathways, and the generation of animal model systems that recreate the disease conditions caused by disruption of the TGF-β signaling network.

**RECENT PUBLICATIONS**


**Hata, A., Lo, R.S., Wotton, D., Lagna, G. and Massague, J. Mutations increasing auto-inhibition inactivate the tumor suppressors Smad2 and Smad4. Nature 388:82-87, 1997.**

**Iavarone, A. and Massague, J. Repression of the CDK ativator Cdc25A and cell-cycle arrest by cytokine TGF-β in cells lacking the CDK inhibitor p15. Nature 387:417-422, 1997.**


*Cell Biology & Genetics*

# Frederick R. Maxfield, Ph.D.

## MEMBRANE TRAFFIC AND CELL MOTILITY

The central focus of the laboratory is the development and use of new optical microscopy and biophysical techniques to study the properties of living cells. We use digital imaging devices, confocal microscopes, and image processing computers to analyze processes occurring at specific sites within cells. Generally, the research covers two areas of biology: (1) membrane trafficking following endocytosis and (2) leukocyte adhesion and motility.

The studies of endocytic trafficking are aimed at developing a complete map and kinetic model for endocytic membrane traffic of receptors, ligands, and membrane components after they enter cells. We are also studying disease-related endocytic processes such as the uptake of large lipoproteins by macrophages leading to atherosclerotic lesions and the interaction of cells with the proteins that form Alzheimer's disease plaques. Each of these uses variations of the basic endocytic processes that we have characterized.

The studies of leukocyte motility are directed towards understanding how intracellular signaling is orchestrated to produce directed cell movement. We have used the migration of human neutrophils in response to chemoattractants as our major experimental system. Several intracellular signaling pathways are stimulated by chemoattractants, which cause the cells to rearrange their cytoskeleton and begin to crawl. We have examined the role of increases in intracellular free calcium, $[Ca^{2+}]_i$, in this process. In one set of studies, we have shown that increases in $[Ca^{2+}]_i$ are required for detachment of neutrophils from extracellular matrix proteins and that activation of a calcium-dependent phosphatase is a key step in this process. Related studies are examining the regulation of cytoskeletal components. Similar processes are used in migration of many cell types, and it is expected that this work will be relevant to migration of metastatic cells.

**RECENT PUBLICATIONS**


**Lawson, M.A., and Maxfield, F.R. Ca2+- and calcineurin-dependent recycling of an integrin to the front of migrating neutrophils. Nature 377:75-79,1995.**

**Mukherjee, S., Ghosh, R.N. and Maxfield, F.R. Endocytosis. Physiol. Rev. 77:759-803, 1997.**


*Biochemistry & Structural Biology*

# Timothy E. McGraw, Ph.D.

## ENDOCYTIC MEMBRANE TRAFFICKING

We study the process of receptor-mediated endocytosis. Cells internalize proteins and macromolecular complexes from the extracellular milieu by endocytosis. Most of the internalized soluble molecules are retained within the cell. Balancing internalization is an endocytic recycling pathway in which most of the membrane internalized by endocytosis is returned back to the plasma membrane. Not all internalized membrane proteins are returned to the plasma membrane. Some membrane proteins are specifically sorted to intracellular organelles (for example, the trans Golgi network). We are currently using molecular cell biological approaches to characterize the targeting information responsible for differential intracellular trafficking of membrane proteins and to identify the endocytic compartments in which the sorting occurs. In addition to constitutive endocytic recycling, some cell types have a regulated recycling pathway. We have recently begun studies of the insulin-regulated endocytic recycling pathway in fat cells. In these cells some membrane proteins (most notably the glucose transporter isoform, GLUT4) traffic through a specialized endocytic pathway. In the absence of insulin the recycling of GLUT4 (and other proteins that traffic through this pathway) back to the plasma membrane is very slow. Insulin stimulates this recycling pathway, thereby inducing a translocation of GLUT4 from intracellular compartments to the plasma membrane. This insulin-induced translocation of GLUT4 to the plasma membrane is responsible for the large insulin-stimulated increase in glucose uptake in fat cells. This reversible translocation of GLUT4 to the plasma membrane is believed to be a key factor in the maintenance of whole body glucose homeostasis. The observation that the insulin-induced translocation of GLUT4 to the cell surface is defective in some patients with insulin-resistant diabetes underscores the importance of understanding this process. We are currently applying biochemical and microscopy methods we have used in studies of constitutive endosomal trafficking to characterize the insulin-regulated pathway in fat cells.

**RECENT PUBLICATIONS**


**Johnson, A., R. Ghosh, R., Dunn, K.W., Garippa, R., Maxfield, F.R., McGraw, T.E. Intracellular trafficking of a chimera between TGN38 and the human transferrin receptor: the cytoplasmic domain of TGN. J. of Cell Biol. 135:1749-1763, 1996.**

**Garippa, R., Johnson, A. and McGraw, T.E. The carboxy cytoplasmic domain of GLUT4 contains a serine-leucine-leucine endocytic trafficking motif. Journal of Biol. Chem. 271:20660-20668, 1996.**


*Biochemistry & Structural Biology*

# Pamela B. Meluh, Ph.D.

## MECHANISMS AND REGULATION OF MITOSIS

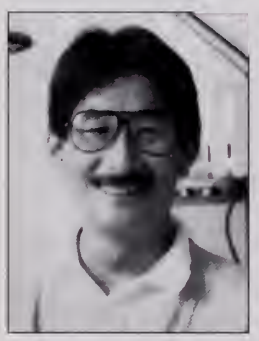
We study mitosis in the budding yeast *Saccharomyces cerevisiae*, a model single-celled eukaryote amenable to a variety of experimental approaches, including molecular, genetic, cell biological, and biochemical techniques. Discoveries made in budding yeast are generally useful in understanding mitosis and the eukaryotic cell, as many fundamental aspects of mitosis are conserved between yeast and higher eukaryotes. Current research focuses on the centromere-kinetochore complex (CKC), a specialized chromatin structure that mediates bipolar attachment of replicated chromosomes to the mitotic spindle and their subsequent segregation during anaphase. Mitotic chromosomes that do not stably attach to the spindle delay the onset of anaphase in a CKC-dependent manner. Therefore, CKCs are also active effectors of the mitotic checkpoint control pathway that monitors spindle assembly. Although many activities have been ascribed to the CKC, neither the manner in which this important multimeric structure is specified and assembled within chromatin, nor the way in which CKC activities are coordinated is understood. We are using *in vivo* crosslinking to study CKC composition and assembly in budding yeast. Our studies have shown that Mif2p and Cse4p, two essential yeast proteins with homology to the mammalian CKC proteins CENP-C and CENP-A, respectively, localize to centromeric DNA. This indicates that aspects of CKC structure, as well as function, are conserved across species. Experiments designed to elucidate the precise functions of Mif2p and Cse4p are in progress. Smt3p, originally identified as a *mif2* suppressor, represents another potential example of conservation within the CKC. Smt3p is a small, essential protein that is distantly related to ubiquitin and defines a new protein family. Like ubiquitin, Smt3p is conjugated to other yeast proteins. Most of Smt3p and its protein targets are nuclear, and *smt3* mutants show defects in mitosis. Current experiments aim to identify Smt3p targets and to understand the mitotic role of Smt3p.

**RECENT PUBLICATIONS**


**Meluh, P. B. and Koshland, D. Evidence that the MIF2 gene of *Saccharomyces cerevisiae* encodes a centromere protein with homology to the mammalian centromere protein, CENP-C. Mol. Biol. Cell. 6:793-807, 1995.**

**Meluh, P.B. and Koshland, D. Budding yeast centromere composition and assembly as revealed by *in vivo* crosslinking. Genes & Dev. 11:3401-3412, 1997.**


*Molecular Biology*



# Takashi Mikawa, Ph.D.

## DIFFERENTIATION AND PATTERNING OF HEART AND BRAIN

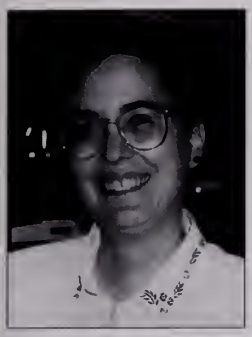
This laboratory is focused on the molecular mechanisms involved in the differentiation and patterning of the cardiovascular and central nervous systems. Both organ systems share a common developmental plan to establish their extremely complicated structures and functions. The developmental plan can be divided into four distinct processes, summarized thusly: Construction of a tubular structure from an epithelial sheet, subdivision of the tube into zones for distinct components of the organ, proliferation and diversification of cells along a perpendicular axis to the epithelial sheet. Both the heart and CNS begin as simple tubes composed of single epithelial cell layers. Within the heart primordia, five distinct subzones are established – endocardial, myocardial, atrial, ventricular, and valvular. Likewise, within the retinal primordia, a projection of the CNS, two subzones, pigmented epithelia and neural retina, are induced. Growth of both organs is characterized by the daughter cells from individual cells of the epithelial sheets, proliferating more vertically while remaining in close association, thereby generating clonal arrays. These arrays take the shape of a cone due to a distinct difference in the mitotic index between external and lumen surfaces. Thus three dimensional spherical structures of both the heart and brain are established by the lateral packing of cone-shaped clonal units. Within a clonal unit, diversification of cell types completes the development of these organ systems. Both neuronal and glial cells are generated within each clone in the brain and similarly in the heart a sub-population of clonally related cardiac myocytes are converted into conducting cells. These findings indicate that each clone is a primary unit for both differentiation and morphogenesis of these organ systems. We are currently analyzing the molecular basis of several of these processes. We are studying the process of subdivision by focusing on the establishment of zones of pigmented epithelium versus neuronal cell fate during development of the retina. Also, we are focusing on diversification within cone units by studying both the conversion of neuronal cells to the glial lineage (neural retina, optic tectum) and the conversion of myocytes to the conducting cell lineage (heart). The major experimental approach involves the use of recombinant retroviruses to modulate the *in vivo* expression of genes encoding growth factors, their receptors, cell-adhesion proteins, and transacting DNA binding proteins including homeodomain proteins.

**RECENT PUBLICATIONS**


**Gourdie, R.G., Mima, T., Thompson, R.P. and Mikawa, T. Terminal diversification of the myocyte lineage generates Purkinje fibers of the cardiac conduction system. Development 121:1423-1431, 1995.**

**Mikawa, T., Hyer, J., Itoh, N. and Wei, Y. Retroviral vectors to study cardiovascular development. Trends in Cardiovas. Med. 6:87-94, 1996.**


*Cell Biology & Genetics*



# Teresa A. Milner, Ph.D.

## RECEPTOR-MEDIATED MECHANISMS FOR NEUROLOGICAL DISORDERS

The aim of my studies is to provide insight on the contribution of specific populations of hippocampal neurons to mnemonic processes and neuropathologies associated with disorders such as Alzheimer's Disease (AD) and seizures in men. The first of my ultrastructural studies has provided evidence that monoamines are major modulators of septohippocampal neurons. The results from these studies also suggest that the transmitter components [acetylcholine and aminobutyric acid (GABA)], via their divergent connectivity with interneurons containing GABA or neuropeptide Y in the hippocampal formation, play differing roles in hippocampal function. These studies demonstrate that selective loss of the cholinergic portion of the septohippocampal pathway partially mimics the pathological changes seen in the autopsied brains of AD patients, but also suggest that AD affects other groups of neurons besides cholinergic neurons. My current studies more directly test: (a) the receptor-mediated mechanisms for monoamine actions on septohippocampal neurons; and (b) the specificity of the expression of low affinity neurotrophin (p75NTR) receptors for the transmitter components of septohippocampal neurons.

My second set of ultrastructural studies has examined the subcellular and cellular distribution of opioids (enkephalins and dynorphins) and their receptors in hippocampal pathways. These studies have provided anatomical evidence for pathway specific modulatory roles of opioids on GABAergic interneurons and have helped elucidate the mechanisms subserving seizure induced changes of opioids. They also suggest that the delta- and mu-opioid receptors, which mediate the actions of enkephalins, are localized to different subpopulations of hippocampal GABAergic interneurons and show that the kappa-opioid receptors, which mediate the action of dynorphins, are located on hypothalamic afferent terminals to the hippocampus. My current grant directly examines: (a) the structural basis for the receptor-mediated actions of opioid on hippocampal neurons; and (b) the selectivity of opioid receptors for either subclasses of GABAergic interneurons or afferent input.

**RECENT PUBLICATIONS**


**Commons, K.G. and Milner, T.A. Localization of delta opioid receptor immunoreactivity in interneurons and pyramidal cells in the rat hippocampus. J. Comp. Neurol. 381: 373-387, 1997.**

**Milner, T.M., Wiley, R.G., Kurucz, O.S., Prince, S.R. and Pierce, J.P. Selective changes in hippocampal neuropeptide Y neurons following removal of the cholinergic septal inputs. J. Comp. Neurol. 386: 46-59, 1997.**


*Neuroscience*

# Malcolm A. S. Moore, D. Phil.

## DEVELOPMENTAL HEMATOPOIESIS

The research aims of this laboratory are to understand the mechanisms of action of both positive and negative regulatory macromolecules that influence proliferation and differentiation of hematopoietic cells. The family of hematopoietic growth factors comprises the three colony-stimulating factors (CSF), fifteen interleukins, and a new family of tyrosine kinase receptor ligands including C-kit ligand and Flk-2 ligand. All are available in recombinant form and are under investigation, *in vitro*, in hematopoietic cell culture systems and *in vitro* in preclinical animal models. In addition, the laboratory is analyzing the hematologic responses of patients receiving certain of these factors (G-CSF, M-CSF, GM-CSF, IL-1, IL-3, IL-6, C-kit ligand) for treatment of congenital, idiopathic, and iatrogenic disorders of hematopoiesis.

We are isolating hematopoietic stem cells from human hematopoietic tissues, including fetal liver, umbilical cord blood, bone marrow, and adult peripheral blood following cyclophosphamide and colony-stimulating factor treatment. Stem cells are being characterized by their ability to initiate long-term, progenitor-generating cultures (5-8 weeks) when cocultured with stromal cells or with combinations of up to seven different cytokines, or by their ability to initiate human hematopoiesis in immunocompromised mice. Ex vivo expansion of stem cells, myeloid progenitors, megakaryocyte progenitors, and dendritic cells is being undertaken under clinical grade conditions in gas-permeable bags or bioreactors, with the objective of autologous transplantation in patients with breast and ovarian cancer, leukemia, and lymphoma. In clinical studies in such patients, we are developing systems for separating normal stem cells from contaminating tumor cells prior to transplantation. Retroviral vectors are being used to introduce new genetic information into hematopoietic stem cells. Improved culture systems allow us to achieve a high transduction efficiency of genes such as the MDR (conferring multidrug resistance) and a dihydrofolate reductase mutant (conferring methotrexate resistance).

**RECENT PUBLICATIONS**


**Flasshove, M., Banerjee, D., Mineishi, S., Li, M-X., Bertino, J.R., Moore, M.A.S. Ex vivo expansion and selection of human CD34+ peripheral blood progenitor cells after introduction of a mutated dihydrofolate reductase cDNA via retroviral gene transfer. Blood 85:566-574, 1995.**

**Albanell, J., Han, W., Mellado, B., Gunawardane, R., Scher, H.I., Dmitrovsky, E., Moore, M.A.S. Telomerase activity is repressed during differentiation of maturation-sensitive but not resistant human tumor cell lines. Cancer Research 56:1503-1508, 1996.**


*Cell Biology & Genetics*

# William A. Muller, M.D., Ph.D.

## MOLECULAR AND CELLULAR BASIS OF INNATE IMMUNITY

My research group is studying the molecular and cellular biology of adhesion molecules responsible for the binding and emigration of leukocytes across vascular endothelial cells. These adhesion events are crucial to the processes of inflammation and atherosclerosis. We have identified and cloned PECAM-1, a molecule that is required for transendothelial migration of leukocytes. We have also cloned VE-Cadherin, an endothelial-specific cadherin that may play a regulatory role in leukocyte emigration.

The roles of these adhesion molecules are being tested using both *in vitro* and *in vivo* models. We have already shown that anti-PECAM monoclonal antibodies or soluble recombinant PECAM blocks inflammation in several models of acute inflammation. These studies were the first to show that transendothelial migration is a distinct step in leukocyte recruitment, which can be dissected on the molecular level *independently* of earlier and later steps. Furthermore, we demonstrated that distinct molecular domains of PECAM are responsible for two separate steps in the emigration process: A hemophilic interaction between immunoglobulin domains 1 and 2 of PECAM on leukocytes with the same domains of PECAM on endothelial cells was crucial for diapedesis. In contrast, an independent interaction of immunoglobulin domain 6 of leukocyte PECAM with components of the subendothelial basal lamina was crucial for migration of leukocytes across the basement membrane once they had passed through the interendothelial junction. Our work was the first to demonstrate that migration across the basal lamina was a distinct step of emigration with its own molecular controls.

In order to study the role of PECAM in chronic inflammatory states such as multiple sclerosis, arthritis, and atherosclerosis, we have generated transgenic mice expressing soluble murine PECAM behind both constitutive and inducible promoters. These mice will be mated into appropriate susceptible strains for long-term studies. We have recently obtained PECAM "knockout" mice, which will be valuable for complementary experiments in these models.

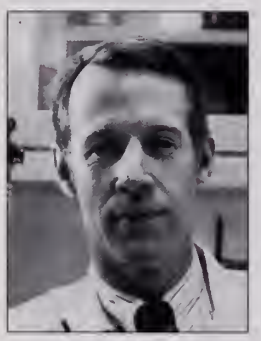
We are currently involved in experiments to understand the various signaling mechanisms by which PECAM functions and how endothelial cell PECAM interacts with VE-cadherin in controlling access of leukocytes to the intercellular junction. In addition to intracellular signaling, we are looking at intercellular signaling, or "cross-talk" between leukocytes and endothelial cells during inflammation. These signals influence the subsequent phenotype and physiology of both cell types and are important determinants in the outcome of the inflammatory response.

**RECENT PUBLICATIONS**


**Liao, F., Ali, J., Greene, T., and Muller, W.A. Soluble domain 1 of platelet-endothelial cell adhesion molecule (PECAM) is sufficient to block transendothelial migration in vitro and in vivo. J. Exp. Med. 185:1349-1357, 1997.**

**Ali, J., Liao, F., Martins, E., and Muller, W.A. Vascular endothelial cadherin (VE-cadherin): Cloning and role in endothelial cell-cell adhesion. Microcirculation 4:267-277, 1997.**


*Immunology*



# Henry W. Murray, M.D.

## IMMUNOREGULATION OF HOST RESPONSIVENESS TO ANTI-*LEISHMANIA* CHEMOTHERAPY

There is no vaccine to prevent human visceral leishmaniasis (VL), a disseminated intracellular protozoal infection, and the efficacy of conventional chemotherapy is declining. Thus, to develop new treatment strategies, this laboratory's research is focused on characterizing the immunoregulatory mechanisms of the successful host response to antileishmanial chemotherapy in a mouse model of VL. This project's objective is to experimentally manipulate these mechanisms *in vivo* in favor of the host receiving treatment to enhance the killing of intracellular *Leishmania donovani* and thereby optimize the host response to chemotherapy.

*In vivo* responses to two clinically appropriate chemotherapeutic probes, antimony (Sb) and amphotericin B, are used to test basic hypotheses to identify critical immunoregulation of the host response to treatment at four levels: (a) the basic antileishmanial pathways of the macrophage, the target host defense cell, (b) effector monocyte influx and action in parasitized tissue, (c) key activating cytokines, and (d) in the intact animal with uncontrolled visceral infection.

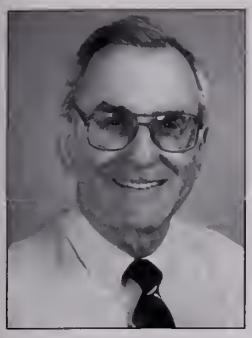
Our aims are to: (1) Determine if toxic nitrogen and/or oxygen intermediates, specific macrophage leishmanicidal mechanisms, are required molecules for Sb-induced intracellular killing. (2) Test if influx of Sb-accumulating monocytes into parasitized tissue granulomas is a determinant of successful chemotherapy and test granuloma-deficient mutant mice. (3) Characterize interleukin 12 (IL-12) in the regulation of the response to chemotherapy. (4) Characterize endogenous host defense mechanisms in the leishmanicidal action of amphotericin B and immunologically enhance amphotericin B's efficacy. And (5) Test the rational application of combination immuno-chemotherapy in uncontrolled visceral infection induced by a clinically relevant Th2 cell-associated state.

**RECENT PUBLICATIONS**


**Murray, H. W., Hariphrashad, J., Coffman, R.L. Behavior of visceral *Leishmania donovani* in an experimentally-induced Th2 cell-associated response model. J. Exp. Med. 185: 867, 1997.**

**Taylor, A., Murray, H.W. Intracellular antimicrobial activity in the absence of interferon-γ: effect of interleukin 12 in experimental visceral leishmaniasis in interferon-γ gene-disrupted mice. J. Exp. Med. 185:1231, 1997.**


*Immunology*



# Ralph L. Nachman, M.D.

## BIOLOGY OF PLATELETS

Endothelial cells play a critical role in thromboregulation by promoting the assembly of a membrane bound fibrinolytic system. Our studies have been designed to characterize the molecular mechanisms controlling this system in health and disease. Cultured endothelial cells synthesize and secrete tissue plasminogen activator which binds to a distinct membrane receptor in a manner that preserves catalytic activity. Circulating plasminogen, the major fibrinolytic zymogen, binds to the endothelial surface and is converted to the membrane bound enzyme plasmin. Lipoprotein (a), an atherogenic lipoprotein particle contains a plasminogen like apolipoprotein (a). This lipoprotein interferes with endothelial cell fibrinolysis by inhibiting plasminogen binding and down regulates plasmin formation. Lipoprotein (a) induces upregulation of plasminogen activator inhibitor mRNA expression and further augments localized thrombogenesis. This system which links chronic thrombogenesis and atherosclerosis may play a major role in the pathogenesis of premature accelerated coronary and cerebral artery occlusive disease. The normal physiologic role of lipoprotein (a) is unknown. Inflammatory cytokines appear to play a major role in regulating this system. Our goals are to define the molecular and cell biologic mechanisms controlling these events.

**RECENT PUBLICATIONS**


**Nachman, R.L. Thrombosis and atherogenesis: Molecular Connections. Blood 79:1897-1906, 1992.**

**Hajjar, K.A. and Nachman, R.L. The role of lipoprotein (a) in atherogenesis and thrombosis. Ann. Rev. Med. 47:423-442, 1996.**


*Cell Biology & Genetics*

# Carl Nathan, M.D.

## MOLECULAR MECHANISMS OF INNATE IMMUNITY

Our goal is to combine genetic, biochemical, and cell biological approaches to the analysis of host defense and inflammation. Specifically, we want to understand how macrophages and neutrophils (PMN) kill microbial pathogens, tumor cells and host cells, and how their capacity to do so is regulated by microbial products like bacterial lipopolysaccharide (LPS), cytokines like interferon-g and tumor necrosis factor (TNF), and proteins of extracellular matrix. We are simultaneously manipulating the genes of the macrophage and the pathogen in order to define the pathways used by activated macrophage to control infection.

*Inducible nitric oxide synthase (iNOS) and NO-resistance genes*. Immunologically activated macrophages use nitric oxide (NO) to injure tumor cells and microbes, including viruses. We have purified, characterized and cloned iNOS, which generates this radical, cloned its promoter, and disrupted the gene by homologous recombination. We are now identifying NO-resistance genes from Mycobacterium tuberculosis and other microbes and investigating their role in pathogenesis.

*Molecular basis of response to LPS*. Mammalian hosts are poised on a hair-trigger to respond to minute quantities of LPS as a signal of infection. Analysis of the amplification path led to the discovery of LPS-mimetic actions of taxol and cloning of an LPS-induced LPS inhibitor. The mechanism of action of each may help unravel the LPS signal transduction cascade.

*Adhesion-dependent responses of PMN*. Adhesion- and spreading-controlled responsiveness to soluble agonists has become a major paradigm in cell biology to explain how extracellular matrix and soluble signals combine to regulate cellular behavior and fate. Studies of PMN responses to TNF helped launch the field. We are now studying how tyrosine kinases help PMN integrate signals from TNF receptors and integrins to reach the decision to discharge large amounts of antimicrobial and tissue-damaging reactive oxygen species and proteases.

**RECENT PUBLICATIONS**


**Jin, Fy., Nathan, C., Radzioch, D., Ding, A. Secretory leukocyte protease inhibitor: a macrophage product induced by and antagonistic to bacterial lipopolysaccharide. Cell 88:417-426, 1997.**

**Chen, L., Xie, Q.-w. and Nathan, C. Alkylhydroperoxide reductase subunit C (AhpC) protects bacterial and human cells against reactive nitrogen intermediates. Molecular Cell. In press, 1998.**


*Immunology*

*Cell Biology & Genetics*

# Janko Nikolic-Zugic, M.D., Ph.D

## T-CELL DEVELOPMENT

***Biology of T-cell development.*** **T-cell life and death.** Thymocytes are subject to massive cell death during development, but their susceptibility of death rests under tight developmental control. We are investigating this control at the level of inducible transcription factors, and their relationship with the apoptosis-regulating Bcl-2 family of proteins. We are also investigating the role of an apoptosis-inducing molecule, FasR/CD95, in T-cell function and autoimmunity. **Regulation of early T-cell development.** Studies are underway to elucidate the role of T-cell receptor (TCR) components in expansion and commitment of early thymocytes. **Terminal differentiation of postselectional thymocytes.** We demonstrated that the majority of $CD4^+$ single-positive (SP), TcR thymocytes still require the thymic environment for final maturation, and are investigating molecular requirements for this process.

***TcR:peptide:MHC contact during antigen recognition and positive selection.*** Only thymocytes whose TcR can bind to self MHC molecules on thymic epithelium will be positively selected to complete maturation. Self peptides, complexed to MHC molecules, profoundly influence positive selection of the T-cell repertoire. Our results suggest that positively selecting self peptides may sometimes share conformational features with the foreign peptides they select the T-cell repertoire for. We continue to investigate the molecular mechanism of TCR:peptide:MHC contact during positive selection and antigen recognition using TcR, and MHC transgenic animals.

***Regulation of CTL responses to peptides.*** We discovered a simple method of eliciting CTLs by *in vivo* peptide priming, useful for immunization against intracellular infections and malignant tumors. We recently observed that this CTL response rests under the control of new immune response genes, and are currently in the process of isolating and characterizing these genes and their mode of action.

**RECENT PUBLICATIONS**


**Dyall, R., Fremont, D. H., Jameson, S.C. and Nikolić-Žugić J. T Cell Receptor (TCR) Recognition of MHC class I variants: Intermolecular second-site reversion provides evidence for peptide/MHC conformational variation. J. Exp. Med. 184:253, 1996.**

**Molano, A., Erdjument-Bromage, H., Fremont D.H., Messaoudi, I., Tempst, P., and Nikolić-Žugić J. Peptide selection by an MHC H-2Kb class I molecule devoid of a central anchor ("C") pocket. J. Immunol. 160:2815, 1998.**


*Immunology*

# Dimitar B. Nikolov, Ph.D.

## STRUCTURAL NEUROSCIENCE

The research in our laboratory is aimed at structural characterization of the molecular mechanisms of signal transduction in the nervous system. We are particularly interested in understanding the processes of detection and recognition of extracellular signals, and the transduction of this information to the inside of the cell by the transmembrane protein machinery. We use X-ray crystallography combined with other biophysical and biochemical techniques to study axon guidance molecules and their receptors, ion channels, and neurotransmitter receptors.

Unraveling the mechanisms of generating and modifying correct connectivity of the $10^{11}$ human neurons is central in understanding the function of the nervous system. Axon guidance molecules are molecules outside the growth cone that assist in selection of the correct pathway and target by changing growth direction. Over the past year, several of them have been identified, characterized, and cloned. Axon guidance cue readout and interpretation present an attractive system for studying both molecular recognition and signal transduction, and we are currently starting biochemical and crystallographic investigations of the netrin and semaphorin families of axon guidance molecules and their receptors.

Ion channels are involved in many physiological processes, such as secretion, regulation of membrane potential, signal transduction, and osmoregulation. They respond to changes in membrane potential or to specific chemical and mechanical signals, by selectively and rapidly enhancing the flux of ions. Investigations using the current methods of protein chemistry, mutagenesis, functional expression, and molecular modeling are beginning to unravel the molecular basis of the essential functions of ion channels, but a definitive mechanistic understanding of their properties ultimately requires three-dimensional structures. We, therefore, are initiating research directed towards the crystallization and high-resolution structure determinations of structurally simpler channels, such as the G-protein activated inwardly rectifying $K^+$ channels.

**RECENT PUBLICATIONS**


**Nikolov, D.B., Chen, H., Halay, E., Usheva, A., Hisatake, K., Lee, D., Roeder, R.G., Burley, S.K. Crystal structure of a TFIIB-TBP-TATA-element ternary complex. Nature 377:119-128, 1995.**

**Nikolov, D.B., Chen, H., Halay, E., Hoffmann, A., Roeder, R.G., Burley, S.K. Crystal structure of human TATA box-binding protein/TATA element complex. Proc. Natl. Acad. of Sci. USA 93:4956-4961, 1996.**


*Biochemistry & Structural Biology*

# Lee Niswander, Ph.D.

## EMBRYONIC GROWTH AND PATTERN FORMATION

Research in my laboratory is focused on understanding the molecular mechanisms that control embryonic vertebrate limb formation. Growth and pattern formation of the developing limb is dependent on cell-cell interactions and much has been learned about the molecular signals mediating this communication. We previously discovered that Fibroblast Growth Factors control vertebrate limb outgrowth. We also showed that the molecular signals for limb growth and pattern formation along the three axes are interdependent and that this mutual interaction could serve to coordinate specification of three-dimensional positional information as the limb grows.

Recent questions of interest in the lab have focused on what are the molecular signals that regulate how limb development is initiated, as well as how the limb stops growing, how are the different patterns of bones formed, how is skeletal differentiation controlled, what normally causes the cells between the digits to die thus freeing the digits, and how is the feather pattern array formed.

**RECENT PUBLICATIONS**


**Zou, H., Wieser, R., Massagué, J., and Niswander, L. Distinct roles of type I BMP receptors in the formation and differentiation of cartilage. Genes and Development 11:2191-2203, 1997.**

**Crowe, R., Henrique, D., Ish-Horowicz, D., and Niswander, L. A new role for Delta in cell fate decisions: establishment of feather pattern. Development 125:767-775, 1998.**


*Molecular Biology*

# Daniel Nussenzweig, M.D., Ph.D.

## CELL BIOLOGY OF G-PROTEIN COUPLED RECEPTORS: TRAFFICKING IN POLARIZED CELLS

Our laboratory is investigating the cellular traffic of G-protein coupled receptors (GPCRs) in polarized epithelial cells. GPCRs make up one of the most important and diverse group of membrane proteins responsible to transduce extracellular signals into cellular responses. They are found in many different types of cells of multicellular organisms, several of which are highly polarized. For the stimuli, either blood-borne, released in a synaptic junction, originated by auto/paracrine secretion, or coming from the environment, to have access to their receptors, it is necessary for the receptors to be expressed on the correct plasma membrane domain of a polarized cell. This localization also is important for the receptors to exert their regulatory function in the correct subcellular domain. The availability of suitable cell models, like the distal nephron derived Madin-Darby canine kidney (MDCK) cell line, allowed investigators to gain knowledge on the fundamental mechanisms involved in the generation and maintenance of cell polarity.

We are currently delineating the mechanisms and molecular determinants that are responsible for the basolateral plasma membrane domain expression of the human calcitonin receptor (hCTR) in MDCK cells. Cell surface-arrival assay of newly formed receptors showed that hCTRs are directly delivered to the basolateral domain. We can predict that there are specific amino acid residues and/or structures within the sequence of hCTRs, that alone or in combination, are presented to the intracellular sorting machinery as signal(s) that direct the final fate of hCTRs during vesicular traffic. To identify these signals, we apply biochemical and cell biological techniques to study expression of receptor mutants. We are also using strategies designed to detect protein-protein intermolecular interactions to identify factors involved in hCTR sorting and targeting to the basolateral membrane.

**RECENT PUBLICATIONS**


**Nussenzveig, D.R., Thaw, C. N., and Gershengorn, M.C. Inhibition of inositol phosphate second messenger formation by intracellular loop one of a human calcitonin receptor. Expression and mutational analysis of synthetic genes. J. Biol. Chem. 269:28123-28129, 1994.**

**Nussenzveig, D.R., Matos, M.F.C., and Thaw, C.N. Human calcitonin receptor is directly targeted to and retained in the basolateral surface of MDCK cells. Am. J. Physiol. 275 (Cell Physiol. 44): C1264-C1276, 1998.**


*Physiology, Biophysics & Molecular Medicine*

# Michiko Okamoto, Ph.D.

## PHARMACOLOGY OF NEUROMUSCULAR BLOCKERS

Dr. Okamoto participates in clinical pharmacologic research related to muscle relaxants which are used during anesthesia. Development of analytical procedure and quantitation of newly developed non-depolarizing type muscle relaxants in patient's biofluid; pharmacokinetic and pharmacodynamic characterization of optically active isomers when existing in patient's biofluid: evaluation of pharmacokinetic and pharmacodynamic interactions of these muscle relaxants with reversible cholinesterase inhibitors that are used to antagonize neuromuscular block by those muscle relaxants during anesthesia, are in focus. Development of *in vitro* experimental procedures to characterize and assess drug interactions which might occur between these muscle relaxants when they are metabolized by plasma cholinesterase, with reversible cholinesterase inhibitors in patient's biofluid, is another focus.

*Neuroscience*

*Pharmacology*

# Richard J. O'Reilly, M.D.

## BONE MARROW TRANSPLANTATION

Our program integrates basic and clinical research focused on genetically influenced interactions between donor and host hematopoietic and lymphoid cells affecting growth and function of histocompatible and incompatible marrow transplants applied to treatment of leukemia and other lethal acquired and congenital disorders of hematopoiesis and immunity. Objectives include: definition of cellular and molecular events which include or prevent graft rejection or Graft-versus-Host Disease (GvHD), definition of biological attributes of a marrow allograft that contribute to enhanced resistance to leukemia in the post transplant period and analysis of cellular interactions that limit or potentiate growth and functional reconstitution of hematopoiesis and immunity in a marrow allograft recipient.

We introduced the use of T-cell depleted marrow grafts for the prevention of GvHD in man, demonstrating that such grafts could be administered from HLA-A,B,D haplotype disparate donors without risk of GvHD. Currently such grafts constitute a curative treatment of choice for children with immunodeficiency diseases. Such transplants prevent or abrogate GvHD in both children and adults with leukemia receiving transplants from matched or partially matched related or unrelated donors.

T-cell depleted marrow allografts are at increased risk of rejection. We identified radioresistant donor-reactive host T-cells as the principal effectors of resistance to engraftment. We have characterized molecular variants of HLA determinants which can be targeted by these host T-cells and are designing studies to identify minor alloantigens that may induce graft rejection. Effective strategies for preventing graft rejection have also been developed, tested in pre-clinical models of transplantation in animals, and thereafter validated in clinical trials.

**RECENT PUBLICATIONS**


**Lacerda, J.F., O'Reilly, R.J. Characteristics of human EBV-specific cytotoxic T-lymphocytes utilized for adoptive immunotherapy of EBV-induced lymphoproliferations in xenografted SCID mice. Annals of Oncology 8(suppl 2):S137-S140, 1997.**

**Papadopoulos, E.B., Carabsi, M.H., Castro-Malaspina, H., Childs, B.H., MacKinnon, S., Boulad, F., Gillio, F., Gillio, A.P., Kernan, N.A., Small, T.N., Szabolcs, P., Taylor, J., Yahalom, J., Collins, N.H., Bleau, S.A., Black, P.M., Heller, G., O'Reilly, R.J., Young, J.W. T-cell depleted allogeneic bone marrow transplantation as post-remission therapy for acute myelogenous leukemia: Freedom from relapse in the absence of graft-vs-host disease. Blood. 91:3, 1083-90, 1998.**


*Immunology*

# Mary Ann Osley, Ph.D.

## REGULATION OF CHROMATIN SYNTHESIS AND FUNCTION IN YEAST

Research in my laboratory is focused on two problems: (i) the regulation of transcription during the eukaryotic cell cycle and (ii) the regulation of chromatin structure and function, particularly as it relates to transcription. We are studying how the transcription of histone genes is controlled during the cell cycle of budding yeast, *Saccharomyces cerevisiae*. These genes encode essential chromosomal proteins whose synthesis is tightly coupled to S phase, the period of DNA replication. Using genetic approaches, we have isolated mutants in which histone gene transcription is uncoupled from the cell cycle. Many of the genes identified in the mutant screens encode transcriptional repressors. Using molecular approaches, we have shown that two of the regulatory proteins – Hir1 and Hir2 – function as transcriptional corepressors, proteins that mediate repression through a site-specific DNA binding protein. These corepressors may function as part of a multiprotein complex, and our current efforts are directed toward identifying other members of the complex and determining how the complex represses transcription. We have also found that the activity of the corepressors is regulated in response to cell cycle signals. The nature of these regulatory signals, and how they lead to periodic inactivation of the Hir corepressors at the G1/S phase boundary is under investigation.

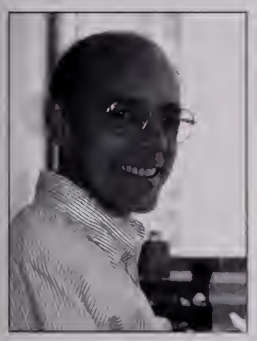
We are also studying how histones affect transcription *in vivo*. Numerous studies have implicated nucleosomes as general repressors of transcription. We have developed two assay systems to study the roles of core histones H2A and H2B in transcriptional repression. Using a combination of genetic and molecular approaches, we are identifying the domains in these histones that are required for transcriptional repression and the nonhistone proteins responsible for these effects.

**RECENT PUBLICATIONS**


**Recht, J., Dunn, B.D., Raff, A., and Osley, M.A. A functional analysis of histones H2A and H2B in transcriptional repression in yeast. Mol. Cell. Biol. 16:2545-2553, 1996.**

**Spector, M., Raff, A., DeSilva, H., Lee, K., and Osley, M.A. Hir1p and Hir2p function as transcriptional corepressors to regulate histone gene transcription in *Saccharomyces cerevisiae*. Mol. Cell. Biol. 17:545-552, 1997.**


*Molecular Biology*



# Lawrence G. Palmer, Ph.D.

## CELLULAR AND MOLECULAR BASIS OF EPITHELIAL ION TRANSPORT

The kidney precisely controls the levels of electrolytes in the plasma. This function is vital, as the body requires a constant internal milieu to function properly. Our laboratory is interested in the cellular and molecular events involved in the transport of $Na^+$ and $K^+$ between blood and urine, and in the hormonal mechanisms underlying the regulation of these transport processes.

These studies have led us to two key transport proteins: $Na^+$- and $K^+$-selective ion channels in the apical membrane of the mammalian cortical collecting tubule. This is the segment of the nephron that is most sensitive to hormones and that oversees the fine control of plasma $Na^+$ and $K^+$. The channels control the reabsorption of $Na^+$ from and the secretion of $K^+$ into the urine. We have identified these transporters using the patch-clamp technique, which allows the study of single channel molecules in living cell membranes. With this approach we can study the properties of individual ion channels-channel density, conductance, and open probability-in the living cell membrane. We are investigating the influence of previous dietary and hormonal history on channel densities. In addition, we are investigating the acute regulation of the channels by membrane voltage, intracellular pH and $Ca2^+$, and phosphorylation.

At the molecular level, we have isolated a cDNA clone for a renal $K^+$ channel, and clones for the epithelial $Na^+$ channel have been identified by others. We are now using these molecular tools to study the long-term control of the channels at the genetic level by measuring changes in mRNA and protein. We are also using site-directed mutagenesis to investigate the parts of the proteins which determine channel conductivity, selectivity and gating. Our long-term goals are to understand at the molecular level how ions move across epithelial cell membranes, and how this movement is regulated to suit the needs of the organism.

**RECENT PUBLICATIONS**


**Palmer, L.G., Sackin, H. and Frindt, G. Regulation of Na channels by luminal Na in the rat cortical collecting tubule. J. Physiol. (London) 509: 151-162, 1998.**

**Choe, H., Sackin, H. and Palmer, L.G. Permeation and gating of an inwardly rectifying potassium channel: Evidence for a variable energy well. J. Gen. Physiol. 112: 433-446, 1998.**


*Physiology, Biophysics & Molecular Medicine*

# Pier Paolo Pandolfi, M.D., Ph.D.

## MOLECULAR AND DEVELOPMENTAL BIOLOGY

The research in my laboratory aims to understand the mechanisms underlying the pathogenesis of myeloid leukemias and to identify molecular events related to commitment, differentiation and maturation of normal myeloid hemopoietic cells. Our model system is acute promyelocytic leukemia (APL), a distinct subtype of acute myeloid leukemia that accounts for more than 10% of all myeloid leukemias. APL is characterized by three unique features: the accumulation in the bone marrow of tumor cells blocked at the promyelocytic stage of myeloid maturation; the association with chromosomal translocations that invariably involve the Retinoic Acid Receptor a (RARa) locus; and the exquisite sensitivity of APL blasts to the differentiating action of Retinoic Acid (RA). The genes involved have been identified by our group and others, and their products characterized. In over 99% of APL cases the translocation fuses RARa to the PML gene. PML is a nuclear protein whose function has not yet been elucidated, and a member of a family of putative transcription factors characterized by the presence of a Zinc Finger domain named RING. RARa is a well-known transcription factor implicated in controlling developmental processes as well as myelopoiesis. In a few cases of APL, the RARa gene translocates and fuses to the PLZF or NPM or NUMA genes.

We are focusing our attention on: 1. The normal function of these genes and how it relates to leukemia and normal myelopoiesis. Through the use of gene ablation technology in mouse ES cells, we have generated, and we are currently characterizing, mice lacking PML and PLZF. Similarly we will generate mice lacking NPM and NUMA functions. 2. The role, *in vivo*, of the chimeric products associated with the leukemic phenotype (PML/RARa, RARa/PML, PLZF/RARa, NPM/RARa, etc.). This is analyzed targeting the expression of the fusion genes in transgenic mice to individual stages in hemopoietic maturation by the choice of appropriate myeloid specific promoters, as well as utilizing an *in vivo* Cre/loxP recombinase mediated system. 3. We have recently discovered a link between leukemias and solid tumors pathogenesis. The gene implicated is a new PML-related RING-finger gene, which we named HPRR (Hepatoma PML Related Ring). In mouse hepatocellular carcinoma, HPRR is fused to the proto-oncogene B-Raf (as PML is to RARa) again forming a "chimeric" product. Due to PML and HPRR functional interactions, the disruption of the their normal functions, caused by the presence of PML/RARa in APL and HPRR/B-RAF in Hepatomas, contribute in a similar manner to the deregulation of growth and differentiation capacities of their target cells leading to cancer.

**RECENT PUBLICATIONS**


**Wang, Z.G. and Pandolfi, P.P. Role of PML in cell growth and the retinoic acid pathway. Science 279:1547-1551, 1998.**

**He, L.Z. and Pandolfi, P.P. Distinct interactions of PML-RARa and PLZF-RARa with co-repressors determine differential responses to RA in APL. Nat. Genet. 18:126-135, 1998.**


*Molecular Biology*

# Joel D. Pardee, Ph.D.

## REGULATION OF CELL MOTILITY

The fundamental intracellular mechanisms involved in cell migration and muscle fiber formation constitute a primary area of laboratory research. For these studies, we have initiated the in vitro reconstitution of a functional intracellular cytoskeleton from isolated actin cytoskeletal proteins. This approach has allowed for analyses of intracellular signals that regulate formation of contractile structures in migratory cells and assembly of nascent myofibrils in cardiac muscle cells.

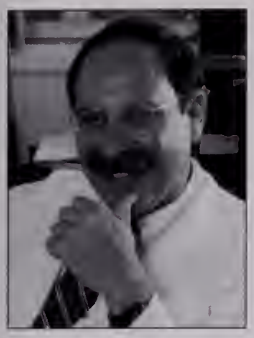
A second area of research is focused on gaining a mechanistic understanding of how rearrangements of the actin cytoskeleton regulate cell migration and cell division in normal and transformed cell types. During metastasis of malignant cells from carcinoma tumors, cell migration results from continual rearrangements of the actin cytoskeleton. We have recently determined that a specific set of actin regulatory proteins are present in tumors and normal migratory cell types, but not in the stationary epithelial cells from which tumors are derived. This has led to studies on the role of these tumor specific motility factors in carcinogenesis.

**RECENT PUBLICATIONS**


**Applegate, D. and Pardee, J.D. Actin-facilitated assembly of smooth muscle myosin induces formation of acto-myosin fibrils. J Cell Biol 117:1223-1230, 1992.**

**Mahajan, R.K. and Pardee, J.D. Assembly mechanism of Dictyostelium myosin II: Regulation by $K^+$, $Mg^{2+}$ and actin filaments. Biochemistry 35: 15504-15514, 1996.**


*Cell Biology & Genetics*



# Gavril W. Pasternak, M.D., Ph.D.

## MOLECULAR PHARMACOLOGY OF OPIOID RECEPTORS

The goal of the laboratory is to understand the receptor mechanism(s) of opioid actions at the molecular, membrane, cellular and systems level. The laboratory utilizes a wide-variety of approaches, including synthetic organic chemistry, biochemistry, cellular and molecular biology and behavioral pharmacology. Over the years, we have developed several useful opiate derivatives which have led to the identification of novel opioid receptor subtypes and their characterization. We also are using molecular biological approaches to obtain novel opioid receptor clones. A major focus has been the correlation of these binding sites with opioid pharmacology, using both antisense and knockout strategies. We recently developed an approach termed antisense mapping to explore the functional significance of splice variants. Antisense techniques also permit the evaluation of the functional significance of partial sequences obtained from RT-PCR, providing an efficient screening process.

Tolerance is a major difficulty encountered in clinical practice. In a series of recent studies we have documented the role of nitric oxide (NO) in morphine tolerance and dependence. Blockade of the enzyme NO synthase with $N^G$-nitro-L-arginine prevents morphine tolerance for up to 4 weeks, the longest time tested. Using antisense mapping, we have identified a specific nNOS splice variant which is associated with tolerance and a different one which has opposite activity, facilitating opioid analgesia. Additional evidence suggests a role for NMDA receptors in the NO cascade. NMDA antagonists also block the development of morphine tolerance, regardless of whether they are noncompetitve, competive or glycine site blockers.

Finally, we are interested in the circuitry of opioid analgesia, particularly in view of the dramatic synergism among regions. Early studies revealed the presence of analgesic synergy between the brain and spinal cord. We have extended this approach to document the presence of synergy between different brainstem regions and have characterized the receptor subtypes responsible for these interactions. Most recently, we have embarked upon studies to define peripheral opioid actions, confirming important interactions between peripheral sites of action and the brain and spinal cord.

**RECENT PUBLICATIONS**


**Kolesnikov Y.A., Pan Y-X., Babey A-M., Jain, S., Wilson, R., and Pasternak, G.W. Functionally differentiating two nNOS isoforms through antisense mapping: Evidence for opposing NO actions on morphine analgesia and tolerance. Proc. Nat. Acad. Sci. USA 94:8220-8225, 1997.**

**Rossi, G.C., Levanthai, L., Bolan, E., and Pasternak, G.W. Pharmacological characterization of orphanin FQ/nociceptin and its fragments. J. Pharmacol. Exp. Ther. 282:858-865, 1997.**


*Neuroscience*

*Pharmacology*

# Dinshaw J. Patel, Ph.D.

## NUCLEIC ACID STRUCTURE AND RECOGNITION

Our research program has focused on the combined application of Nuclear Magnetic Resonance (NMR) and Molecular Dynamics (MD) calculations to determine the solution structure and interactions involving nucleic acids. Ongoing projects include structure determination of multistranded DNA architectures adopted by telomeric and triplet repeat disease sequences which are known to be stabilized by base triples, tetrads and triads. We also continue to structurally characterize site-specific stereoisomeric covalent carcinogenic DNA adducts with a new emphasis on mammary and testes tumor carcinogens and their interactions with domains f damage recognition proteins.

A new research program has been initiated on RNA structure and recognition through studies of RNA tertiary folds identified through in vitro selection procedures for their ability to bind with high affinity and specificity to cofactors, antibiotics, peptides and proteins. We have recently solved the solution structures of RNA aptamers bound to cofactors FMN and AMP and the aminoglycoside antibiotic tobramycin and in the process have identified unprecedented RNA tertiary folds and ligand binding sites.

We are also characterizing the solution structures of specific peptide-RNA complexes that play a key role in the life cycle of immunodeficiency (BIV-HIV-1) and leukemia (HTLV-1) viruses and bacteriophages (P22). Our recent solution structures of BIV-Tat peptide-TAR RNA and HIV-1 Rev peptide-RRE RNA aptamer complexes define how a b-sheet and a-helix, respectively are accommodated within a widened major groove, with both arginine-rich peptides and their RNA targets undergoing conformational transitions on complex formation. Similar studies have defined the structure of the P22 N peptide-box B RNA complex involved in transcriptional antitermination and are being extended to the HTLV-1 Rex peptide-RNA complex to define the details of the intermolecular interactions.

**RECENT PUBLICATIONS**


**Ye, X., Gorin, A., Ellington, A.D. and Patel, D.J. Deep penetration of an a-helix into a widened RNA major groove in the HIV-1 Rev peptide-RNA aptamer complex. Nature Struct. Biol. 3:1026-1033, 1996.**

**Cai, Z., Gorin, A., Frederick, R., Ye, X., Hu, W., Majumdar, A., Kettani, A. and Patel, D.J. Solution structure of p22 transcriptional antitermination N peptide-box B RNA complex. Nature Struct. Biol. 5:202-212, 1998.**


*Biochemistry & Structural Biology*

# Nikola P. Pavletich, Ph.D.

## STRUCTURAL BIOLOGY OF ONCOGENES AND TUMOR SUPPRESSORS

Our research group is interested in the structural biology of pathways that control cell growth and proliferation, with particular emphasis on pathways whose alteration contributes to cancer. Currently, much of our research is focused on the p53, retinoblastaoma (Rb), and $p16^{MTS1}$ tumor suppressors, which are among the most frequently altered genes identified in human cancer to date. This focus has also led to our study of the eukaryotic cell cycle and, specifically, the cyclin dependent protein kinases (Cdks), as they are necessary for cell growth and thus they are downstream targets for most growth regulatory pathways.

Our aim is to determine the high resolution three dimensional structures of the key proteins in these pathways, in order to understand how they function, how their structure and function is altered in cancer, and how specific growth-controls can be restored in cancer.

**RECENT PUBLICATIONS**

**Russo, A.A., Jeffrey, P.D., Patten, A., Massague, J., Pavletich, N.P. Crystal structure of the $p27^{Kip1}$ cyclin-dependent kinase inhibitor bound to the CyclinA-CDK2 complex. Nature 382:35-331, 1996.**

**Lee, J.-O., Russo, A.A., Pavletich, N.P. Structure of the Relinoblastoma tumor-suppressor pocket domain bound to a peptide from HPV E7. Nature 391:859-865, 1998.**

*Biochemistry & Structural Biology*

# Howard T. Petrie, Ph.D.

## DEVELOPMENTAL IMMUNOLOGY

T cell lymphopoiesis occurs in the thymus from bone marrow-derived precursors. Each thymic precursor undergoes multiple differentiative and proliferative events. Like other tissues, T cell development proceeds through checkpoints at which some cells survive to continue differentiation, while others undergo programmed cell death. Analyzing events that regulate these fates is the focus of research performed in this laboratory.

Eight major stages of T cell development can be identified. Our previous studies show that transition between these phases is generally marked by TCR gene rearrangement events. Further, mutations in genes required for TCR expression results in developmental arrest at defined stages of differentiation. Together, such findings have led to the belief that signaling through the TCR is an inductive signal in thymocyte differentiation. However, more recent studies from our laboratory suggest that this conclusion may be incorrect, and that while signaling through the TCR (or pre-TCR) is required for survival, it does not induce differentiation *per se*. Consequently, we are studying other potential mediators of differentiation. For instance, a number of integrins and other adhesion molecules are known to be differentially regulated during T lymphocyte development, including those thought to regulate proliferation and survival in other tissues. So far, we have characterized the role of one of these, the $\alpha6\beta4$ integrin receptor, using both germline mutant and transgenic approaches, and find that this receptor has a clear role in regulation of differentiation at the $CD4^-8^-$ to $CD4^+8^+$ transition. Such studies are presently being extended to an integrated model for thymocyte differentiation based on convergent differentiative signals.

As mentioned above, proliferation and cell death are frequently coincident during T cell development. We have recently shown that the archetypal inhibitor of cell death in mammals, Bcl-2, can also inhibit cell cycle progression in a manner that may influence survival; this finding has since been confirmed by several other groups. We now find that Bcl-2 profoundly influences the composition of complexes formed by the pRb and E2F families of proteins under conditions that influence cell growth, differentiation, cell cycle withdrawal, or cell death. Experiments aimed at understanding the mechanisms of this effect, and their influence on thymocyte proliferation and survival, are also underway.

**RECENT PUBLICATIONS**

**Mazel, S., Burtrum, D., and Petrie, H.T. Regulation of cell division cycle progression by *bcl*-2: a potential mechanism for the inhibition of programmed cell death. J. Exp. Med. 183:2219-2226, 1997.**

**Tourigny, M., Mazel, S., Burtrum, D.B., and Petrie, H.T. TCR-β gene recombination: dissociation from cell cycle regulation and developmental progression during T cell ontogeny. J. Exp. Med. 185:1549-1556, 1997.**

*Immunology*

# Virginia M. Pickel, Ph.D.

Problem Under Study:

To determine the cellular basis for chemical signaling between neurons in health and disease.

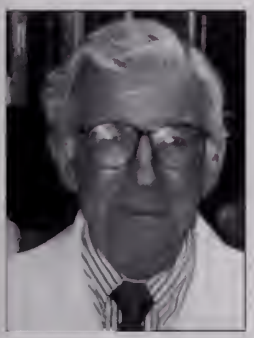
The long range goal of this research is to determine cellular sites for functional communication between neurons in brain regions associated with emotional control of automatic function and the rewarding and adverse actions of opiates. This broadly based research program is multidisciplinary and is based on light and electron microscopic immunocytochemistry, in situ hybridization and intracellular physiology. These methods are applied in three separate but related research areas. The first is directed towards understanding mechanisms involved in cardiorespiratory function through circulating hormones and central neural pathways. These specifically include imput from the central nucleus of the amygdala, an important brain center involved in the integration of emotional and stress responses to external stimuli. The second research area focuses on establishing the basis for interactions between opiates and catecholamines in forbrain regions associated with reward and motor functions. The third research area examines drug and lesion-induced changes in postnatal development and adult circuitry of opiate containing neurons. Disruptions of pathways that are under investigation have been implicated invarious psychiatric disorders and in both the beneficial and adverse affects of antipsychotic drugs. such as haloperidol. The combined effort of these projects in the rat animal model will provide information relevant to a better understanding of the mechanisms of cellular interactions in normal human brain and for understanding and drug treatment of disorders associated with alterations in these tranmitter systems.

**RECENT PUBLICATIONS**


**Nirenberg MJ; Vaughan RA; Uhl GR; Kuhar MJ; Pickel VM. The dopamine transporter is localized to dendritic and axonal plasma membranes of nigrostriatal dopaminergic neurons. J Neurosci Jan 15;16(2):436-47, 1996.**

**Svingos,A.L., Clarke, C.L. and Pickel, V.M. Cellular sites for activation of delta opioid receptors in the nucleus accumbens shell: Relationship with Met-enkephalin. J. Neurosci. 18:1923-1933, 1998.**


*Neuroscience*



# Fred Plum, M.D.

## MULTIDISCIPLINARY STUDIES OF HUMAN CONSCIOUSNESS

Our principal research work involves a multidisciplinary team studying various aspects of the neurology of human consciousness. Included are neuropsychologists, electrophysiologists, cognitive neuroscientists and experts on several aspects of brain imaging. The last category includes positron emission tomography (PET), functional magnetic resonance imaging (FMRI) and, with collaborators from New York University, brain magnetometry. The central goals of imaging studies are to outline the chronology and functional anatomy of cerebral structures processing normal conscious awareness. Secondary goals are to distinguish similar time and spatial dimensions of normal preconscious cerebral activity compared to those of conscious perception. Baseline imaging studies of normal conscious mechanisms plus quantitative analysis of the vegetative state are now completed. Next steps are aimed at identifying the anatomy and functional evolution of the consciousness modality. Similar studies of patients with global or focal brain lesions impairing self awareness are conducted as the opportunity arises. Psychological and neurophysiologic studies relating to subjective conscious awareness are mentioned elsewhere in this volume under Dr. Jonathan Victor's research program.

**RECENT PUBLICATIONS**


**Plum, F. Extension of Fundamental Stroke Research Into Clinical Care. Clin. Neurosci. 4: 175-8, 1997.**

**Goldman, S., Plum, F. Compensatory Regeneration of the Damaged Adult Human Brain: Neuroplasticity in a Clinical Perspective. Adv. Neurol. 73: 99-107, 1997.**


*Neuroscience*

# Jerome B. Posner, M.D.

## PARANEOPLASTIC SYNDROMES

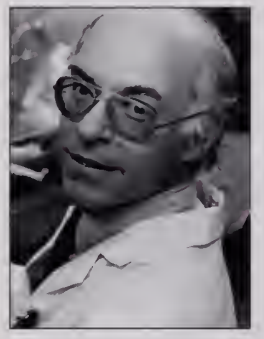
Investigators in this laboratory screen the serum and cerebral spinal fluid (CSF) of patients with paraneoplastic syndromes (nervous system degenerations associated with cancer) looking for the presence of antibodies that specifically react with antigens of the nervous system and with the underlying cancer (onconeural antigens). The hypothesis is that an immune attack against the antigen(s) in the cancer has the dual effect of inhibiting growth of the cancer and of damaging or destroying portions of the nervous system. When such antibodies are identified in serum of CSF, we attempt to characterize the antigens using both standard immunologic and molecular biologic techniques. To date, three neurological syndromes with three different antibodies, anti-Yo, anti-Hu and anti-Ri have been identified, their clinical characteristics defined and the gene coding for the antigens cloned and characterized.

**RECENT PUBLICATIONS**


**Posner JB. Anti-Hu autoantibody associated sensory neuropathy/encephalomyelitis: a model of paraneoplastic syndrome. Perspect Biol Med 38:167-81, 1995.**

**Sillevis Smitt PA; Manley GT; Posner JB. Immunization with the paraneoplastic encephalomyelitis antigen HuD does not cause neurologic disease in mice. Neurology 45:1873-8, 1995.**


*Neuroscience*



# David N. Posnett, M.D.

## HUMAN MOLECULAR IMMUNOBIOLOGY

This laboratory focuses on basic mechanisms of human immunological disease and basic questions of immune function such as recognition of peptide antigens and superantigens (SAG) by T cell antigen receptors (TCR).

Our studies evolved from work in the early 1980s, in which some of the first antibodies to human T cell antigen receptors were described and used to define the chemical nature of the TCR. This led to the development of a large panel of monoclonal antibodies with specificity for various TCR V determinants produced in various laboratories. These reagents are now commercially available and widely used for basic and clinical studies as well as for diagnostic purposes. They were recently analyzed in the first International Workshop on TCR antibodies organized by Dr. Posnett. They are useful to examine the TCR repertoire in humans. For example, we currently use them to study a subset of CD8 T cells, that lack expression of the important co-stimulatory molecule CD28, and which are often clonally expanded. These expansions are sometimes dramatic, such that a single clone can represent up to 50% of all T cells in the blood! These cells are cytotoxic effector cells or "killer" T cells. We can now easily identify them based on their phenotype and study their function in normal humans and in disease.

The earlier work led to the study of superantigens which typically have specificity for TCR V regions. SAG are produced by unrelated microbes and even plants. We have studied the molecular sites at which SAG interact with TCRs and found that the TCR residues involved are variable depending on the SAG. Thus unrelated organisms have independently evolved SAG molecules that are all able to bind to TCRs in unorthodox and distinct ways. Apparently, vigorous T cell stimulation benefits this organisms. Bacterial superantigens, such as Toxic Shock Syndrome Toxin, are well appreciated as agents of human disease. However, viral superantigens are not well recognized in humans. There is a single well documented example of a virus which produced SAG: the mouse mammary tumor virus (MMTV). This HIV-like retrovirus is vertically transmitted via maternal milk and the SAG encoded in the 3'ORF is absolutely required for establishing persistent infection in the neonatal host. We now believe that human Herpesviruses are also associated with SAG (Dobrescu et al, Cell, 1995). Thus, the main focus in this lab is currently on the molecular biology of Herpesvirus SAG.

Our studies on HIV have centered on a subset of CD4 negative infected T cells which may be protected against apoptosis. We hypothesize that much of the loss of CD4 cells in AIDS is a consequence of host responses directed at uninfected bystander T cells.

**RECENT PUBLICATIONS**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**Hodtsev, A.S., Choi, Y., Spanopoulou, E., and Posnett, D. N. Mycoplasma superantigen is a CDR3-dependent ligand for the T cell antigen receptor. J. Exp. Med. 187:319-327, 1998.**


*Immunology*

# Mark Ptashne, Ph.D.

## MECHANISM OF GENE REGULATION

We study fundamental mechanisms of gene regulation – how proteins bind to DNA and turn transcription of genes on and off. Many of our ideas were first formulated in studies of genes of bacteria and of phage lambda. Those studies revealed, among other findings, how proteins recognize specific sites on DNA; the importance of cooperative binding of proteins to DNA to create efficient "switches"; and the fact that gene activation is mediated by a contact between the activator's "activating region" and RNA polymerase. We now study these mechanisms as elaborated in eukaryotes – in yeast, Drosophila, and in mammalian cells. We have recently argued that a mechanism of gene activation – which we call recruitment – is used to control many genes in prokaryotes and in eukaryotes, and we are now testing various aspects of that idea. According to this idea, the interaction between a DNA-bound activator and the transcriptional machinery is "velcro"-like; that is, the interaction merely has to provide binding energy to bring the machinery to DNA. And so we are probing the nature of activator-transcriptional machinery contacts in a variety of genetic and biochemical experiments. We are also studying mechanisms of gene activation that dispense with traditional activators, and we are attempting to understand how eukaryotic repressors work. We are also studying the roles of histones and their modifiers in these various processes. Recruitment mediated by velcro-like interactions explains many aspects of gene regulation, including how regulators can work in different combinations to appropriately control disparate genes. We suggest that various features of this mechanism ensure "evolvability" of complicated genetic regulatory networks, and that the principles involved are found in other networks found in cells, including, for example, intracellular signal transduction pathways.

**RECENT PUBLICATIONS**


**Barberis, A., Pearlberg, J., Simkovich, N., Farrell, S., Reinagel, P., Bamdad, C., Sigal, G., and Ptashne, M. Contact with the Pol II holoenzyme suffices for gene activation. Cell 81:359-368, 1995.**

**Ptashne, M. and Gann, A. Transcriptional activation by recruitment. Nature 386:569-577, 1997.**


*Molecular Biology*

# Keith Purpura, Ph.D.

## THE ROLE OF TEMPORAL CODES IN CORTICO-CORTICAL COMMUNICATION

In order to understand the injured brain, it is necessary to understand the functioning of the brain as a whole. Many neurological disorders can be understood as the breakdown of the normal flow of information along the pathways in the brain. Brain injuries, such as head trauma, stroke and degenerative diseases such as Alzheimer's, disconnect these pathways leading to impaired brain function. Understanding the mechanisms which link separate brain areas to produce their integrated functions is as necessary as understanding the specific process by which the damage occurs. The long range goal of our research is to provide a basic understanding of how brain regions communicate. This goal has the potential for translation into targeted therapeutic approaches to problems of abnormal brain function.

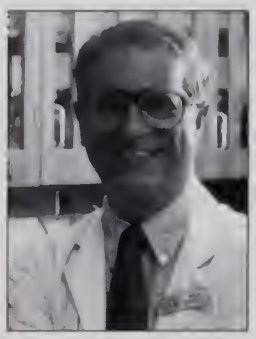
One way for two brain regions to communicate is through a precisely paced choreography of brain cell activity in the two regions, much like a tango. Alternatively, the average level of activity in the two brain regions may be enough, just as the overall amount of arm, leg, and torso gyrations is enough to convey excitement at a dance party. Our research investigates both modes of information exchange (the two temporal codes) by recording simultaneously the activity of brain cells in two brain regions while a visual task is being performed. Single and multiunit electrophysiological recordings are made simultaneously in two cortical regions (V1/V4, V1/IT and V4/IT). Spike trains and local field potentials recorded in the two visual areas are analyzed for crosscorrelation structure. This analysis can reveal different modes of temporal processing such as oscillations or synchronized bursting. Our goal is to determine if precise patterns of activity predominate more for visual recognition or for visual attention, and the role played by average levels of activity in mediating the brain's information superhighway.

**RECENT PUBLICATIONS**


**Purpura, K.P. and Schiff, N.D. The thalamic intralaminar nuclei: a role in visual awareness. The Neuroscientist 3:8-15, 1997.**

**Victor, J.D. and Purpura, K.P. Nature and precision of temporal coding in visual cortex: a metric-space analysis. J. Neurophysiol. 76: 1310-1324, 1997.**


*Neuroscience*



# Marcus M. Reidenberg, M.D.

## CLINICAL PHARMACOLOGY AND PHARMACOLOGY OF GOSSYPOL

Current research is focused on the pharmacology of gossypol, a compound with potential as an anticancer drug and also as a contraceptive pill for men. The action of this compound in men to suppress sperm was accidentally discovered in China. The Chinese then tried to develop it as a contraceptive pill for men. Some men in the study developed low serum potassium and the Chinese abandoned the drug. However, low serum potassium occurs spontaneously in men in China. We found that low potassium in China was due to the Chinese environment and not to Chinese genes. We have found that gossypol inhibits the enzyme that oxidizes cortisol to cortisone (inactivating the cortisol). Inhibition of this enzyme would lead to excessive cortisol effect on the kidney causing increased excretion of potassium and lowering body potassium. We then discovered many other compounds, common in foods from plants, that also inhibit this enzyme.

To study the effects of gossypol in humans, we initiated a series of clinical trials of gossypol in patients with advanced cancers.A 10%-15% partial response rate was found in adrenocortical cancer and glioblastoma. A trial in metastatic breast cancer is ongoing. At the laboratory level, we are trying to learn the mechanism of the antineoplastic effect of gossypol. A hypothesis is that gossypol inhibits the anaerobic form of lactic dehydrogenase and further impairs the energy sources of ischemic cancers. We are pursuing this biochemical hypothesis. We are also using genetic techniques to try to discover some of the genes in the pathway by which gossypol kills cancer cells as another way to learn its mechanism of action.

**RECENT PUBLICATIONS**


Igueros, M., Jeoung, D., Tang, B., Hochhauser, D., Reidenberg, M.M., and Sonenberg, M. Gossypol inhibition of mitosis, cyclin D1 and Rb protein in human mammary cancer cells and cyclin-D1 transfected human fibrosarcoma cells. Brit. J. Cancer, 76:21-28, 1997.

Bushunow, P., Reidenberg, M.M., Wasenko, J., et al. Gossypol treatment of recurrent adult malignant gliomas. Naunyn-Schmiedeberg's Archives of Pharmacology, (in press) (abstract), 1998.


*Pharmacology*

# Donald J. Reis, M.D.

**Molecular and Cellular Mechanisms by which Central Pathways Control Autonomic Function and Behavior; Novel Receptors and Transmitters in Brain; Mechanism of Neuronally Mediated Neuroprotection**

My Laboratory, in the Division of Neurobiology, is studying the neuronal, chemical and molecular genetic organization of systems within the brain which regulate the autonomic nervous system and behavior. Such systems, largely contained within the brainstem, play critical roles in regulating blood pressure, cerebral blood flow and metabolism, sleep and wakefulness and are targets for hormones and drugs which influence behavior. Activation of these pathways protect the brain from ischemic injury and are major targets of psychoactive drugs. The Laboratory is multidisciplinary with scientists trained in neuroanatomy, electrophysiology, neuroanatomy, neurochemistry, pharmacology and molecular biology strongly interacting. Present areas of interest include:

1. *Central neurogenic neuroprotection*. We have discovered that brief excitation of pathways within brain can markedly reduce the neuronal death induced by ischemia (stroke) and excitotoxins. The cellular mechanisms through which activation is mediated involve profound modulation of immune mechanisms in brain and alterations of neuronal excitability. Studies are being undertaken to analyze the genes and proteins which may be expressed to protect the brain from injury, including cytokines, transcription factors and specific neurotransmitters and their receptors.

2. *Oxygen-sensing Neurons in Brain*. The pacemaker neurons in the rostral ventral medulla responsible for maintaining of blood pressure, we have discovered, are chemically distinct, and may be the true oxygen sensors in the brain, initiating widespread patterns of neuronal activation to changes in atmospheric oxygen. Electrophysiological and molecular studies are underway in vivo and in brain slices and in cultured neurons to identify the molecular mechanisms by which the neurons sense oxygen.

3. *Central neural regulation of the cerebral circulation*. While most contemporary methods for functional imaging examine changes in cerebral blood flow the neuronal mechanisms responsible for transduction of neural signals into changes in flow are not known. We are investigating, using autoradiographic, tract tracing, and electrophysiological methods the identity of pathways, effective signals and neuronal substrates of this neurogenic regulation of this vital vascular bed particularly by hypoxia.

4. *Novel central neurotransmitters/receptors*. A novel and widespread receptor, the imidazoline receptor, responsible for the actions of antihypertensive agents and mediating neuroprotection in stroke is being cloned, its distribution and regulation mapped, and signal transduction pathways elaborated. We have discovered one novel transmitter, agmatine (decarboxylated arginine) for the receptor with its synthesis, storage and function being investigated. Other transmitter candidates are being isolated.

**RECENT PUBLICATIONS**


Galea, E., Golanov, E.V., Feinstein, D.L., Kobylarz, K.A., Glickstein, S.B. and Reis, D.J.: Cerebellar stimulation reduces inducible nitric oxide synthase expression and protects brain from ischemia. Amer. J. Physiol. 274:2035-2045, 1998.

Reis, D.J. and Regunathan, S.: Agmatine: A novel neurotransmitter? Adv. Pharmacol. 42: 645-649, 1998.


*Neuroscience*

# Marilyn D. Resh, Ph.D.

## MEMBRANE INTERACTIONS OF FATTY ACYLATED ONCOPROTEINS

My research interests concern the molecular mechanism of cellular transformation by RNA tumor viruses. The long term objective is to understand how oncogene products associate with cellular membranes and why this interaction is important for transformation. Our focus is on members of the Src family, a group of myristylated membrane-bound tyrosine protein kinases. During the past several years, my laboratory has established in vitro systems to study the biosynthesis, fatty acylation and membrane insertion of Src kinases. We have identified a novel membrane binding motif within the Src protein consisting of myristate plus a cluster of basic residues. Membrane association results from synergism provided by: hydrophobic insertion of myristate into the lipid bilayer and electrostatic interaction of the positively charged amino acids with negatively charged head groups of acidic membrane phospholipids. This "myristate + basic" motif is also found in the Gag structural proteins of certain retroviruses. Our laboratory has recently shown that the myristate + basic domain mediates plasma membrane targeting of HIV-1 Gag, thereby allowing Gag to function in the formation and budding of virions. We are currently studying the molecular mechanisms involved in retroviral particle formation at the plasma membrane.

A related area of interest concerns signaling proteins modified by the 16-carbon fatty acid palmitate. We have shown that several Src-related proteins are dually fatty acylated with both myristate and palmitate. The palmitylation reaction is dynamic and reversible, and regulates the ability of Src family members to bind to membranes and participate in signaling. Our most recent experiments are focused on understanding how dual fatty acylation mediates intracellular protein trafficking, membrane targeting, and intracellular signal transduction.

**RECENT PUBLICATIONS**


**Van't Hof, W. and Resh, M.D. Rapid plasma membrane anchoring of newly synthesized p59fyn. J. Cell Biol. 136: 1023-1036, 1997.**

**Wolven, A., Okamura, H., Rosenblatt, Y., and Resh, M.D. Palmitylation of Fyn is reversible and sufficient for plasma membrane association. Mol. Biol. Cell 8: 1159-1173, 1997.**


*Biochemistry & Structural Biology*

*Cell Biology & Genetics*

# Arleen B. Rifkind, M.D.

## MOLECULAR TOXICOLOGY

My laboratory is investigating mechanisms for toxic and protective responses of cells to the environmental pollutants dioxin (TCDD) and polychlorinated biphenyls. These compounds affect cell function by activating a cytosolic receptor, the *Ah* receptor, a ligand activated transcription factor which, together with its heterodimerization partner ARNT, activates transcription of several genes. Cytochrome P450 (CYP)1A1, a subfamily member of the CYP CYP enzyme superfamily has been best characterized. *Ah* receptor activation is required for all of the biochemical and toxic effects of TCDD. TCDD toxicity includes involution of the thymus gland, hyperkeratinization, edema formation, wasting, tumor promotion and death. How these diverse effects are caused and related and the basis for the large species differences in responses are some of the persisting mysteries associated with TCDD and other *Ah* receptor ligands.

Our current research focuses on the role of CYP1A induction in TCDD toxicity, using the chick embryo as our major animal model. While CYP1A enzymes activate some carcinogens, i.e. benzo(a)pyrene, to cytotoxic and genotoxic metabolites, TCDD is neither extensively metabolized nor genotoxic. We purified, cloned and sequenced two TCDD-induced avian CYP1A enzymes, which have been classified as CYP1A4 and 1A5. CYP1A5 is unusually active in metabolizing the endogenous membrane fatty acid, arachidonic acid, to biologically active epoxides (EETs); its expression is restricted to liver and kidney while CYP1A4 is present in liver, kidney, heart and vasculature. We hypothesize that CYP1A induction may lead to changes in signal transduction by altering the metabolism of endogenous cellular constituents.

Current and future projects include: heterologous expression of the two avian CYP1A enzymes, identification of the amino acid determinants of the high arachidonate epoxygenase activity of CYP1A5; characterization of the regulatory regions of the CYP1A4 and 1A5 genes; investigation of the effects of CYP-dependent arachidonic acid metabolism on gene transcription, intracellular calcium, membrane lipid composition and cell signalling, and the biologic significance of the differences in tissue distribution of the two CYP enzymes.

**RECENT PUBLICATIONS**


**Gilday, D., Gannon, M., Yutzey, K., Bader, D., and Rifkind, A.B. Molecular cloning and expression of two novel avian cytochrome P450 1A enzymes induced by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. J. Biol. Chem. 271:33054-33059, 1996.**

**Gilday, D., Bellward, G.D., Sanderson, J.T., Janz, D.M. and Rifkind, A.B. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin induces hepatic cytochrome P450-dependent arachidonic acid epoxygenation in diverse avian orders: Regioisomer selectivity and immunochemical comparison of the TCDD-induced P450000s to CYP1A4 and 1A5. Toxicol. Appl. Pharmacol. 149: (in press), 1998.**


*Pharmacology*

# Richard A. Rifkind, M.D.

## CELL GROWTH AND DIFFERENTIATION

The research aims of this laboratory are to elucidate the cellular and molecular mechanisms responsible for the induced differentiation of transformed (neoplastic) cells. The principal model system is the murine erythroleukemia cell (MELC), which can be induced to cease cell division and to differentiate into phenotypically normal red blood cells by exposure to any of a number of chemical agents, designed and synthesized by the research program, such as hexamethylene bisacetamide (HMBA) and a family of even more potent hybrid polar compounds, derived from the structure of HMBA. Candidate molecular targets for the cellular action of these agents, including enzymes of the histone deacetylase family. Down-stream effects include significant modulations of the molecular machinery controlling the cell division cycle, and the transcription of genes specific for the developmental program of the particular cell type, such as the globin genes for erythroid cells.

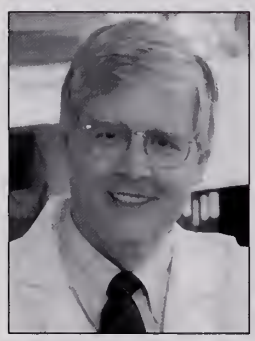
At the same time the laboratory is pursuing the development and evaluation of hybrid polar compounds as potential chemotherapeutic agents for the prevention and control of cancers. Phase I and II studies have demonstrated proof-of-principle effectiveness of this family of compounds, but have also indicated the limited usefulness of the prototype, HMBA, due to clinical toxicities. Pre-clinical studies of several highly potent derivatives are in progress at this time, with the goal of clinical trials in the near future.

**RECENT PUBLICATIONS**


**Richon, V.M., Russo, P., Venta-Perez, G., Cordon-Cardo, C., Rifkind, R.A., and Marks, P.A. Two cytodifferentiation agent-induced pathways, differentiation and apoptosis, are distinguished by the expression of human papillomavirus 16 E7 in human bladder carcinoma cells. Cancer Research 57:2789-98, 1997.**

**Richon, V.M., Emiliani, S., Verdin, E., Webb, Y., Breslow, R., Rifkind, R.A., and Marks, P.A. A class of hybrid polar inducers of transformed cell differentiation inhibits histone deacetylases. Proc. Natl. Acad. Sci. USA 95:3003-07, 1998.**


*Cell Biology & Genetics*



# Hugh D. Robertson, Ph.D.

## RNA STRUCTURE AND FUNCTION

Our work concerns the structure and function of biologically active RNA molecules. The primary focus is the RNA of the agent which causes human delta hepatitis. This pathogen replicates via a rolling circle mechanism, utilizing two RNA-catalyzed cleavage activities (ribozymes) which are built into the genomic and complementary antigenomic strands of delta agent's RNA. The linear progeny RNAs so produced are then ligated to form circles. We are studying the structure and function of these ribozymes, as well as the RNA ligase activity which circularizes their cleavage products. We are also studying the use of targeted cleavage by delta and other ribozymes in therapeutic applications; and the interaction of host protein factors with delta agent RNAs. Our methods, which are also being used to map the structure of the IRES domain of hepatitis C virus RNA, include direct RNA sequence analysis, RNase protection studies using added proteins or RNAs; and a method for probing RNA tertiary structure using UV-induced RNA-RNA crosslinking.

Work on delta ribozymes includes the isolation and separation into enzyme and substrate subdomains of the delta ribozyme elements. Detailed studies show that the two delta ribozymes— encoded by the genomic or antigenomic strand—are quite different despite extensive (80%) sequence identity. Furthermore, RNA ligase studies have shown that a host enzyme—the yeast-type tRNA ligase recently implicated in host mRNA as well as tRNA splicing—is likely to be the activity utilized in vivo to circularize delta RNA. We are studying this delta ligation reaction in transfected liver cells.

Research on therapeutic applications of ribozymes involves re-targeting these activities so that they can cleave harmful RNAs. The delta ribozymes are being re-targeted to cleave several disease-causing viral RNAs, as is the cellular ribozyme RNase P. These same techniques are being applied to a study on targeted cleavage of cellular mRNAs to control expression of, for example, opioid receptor mRNAs in a collaborative study with Dr. C. Inturrisi of the CUMC Pharmacology Department.

Protein: RNA binding studies involve delta genomic RNA and a host protein kinase, called PKR, which is activated by RNA. PKR binds the delta RNA at a specific site containing an element of local tertiary structure, and could be the kinase responsible for reported phosphorylation of a delta-encoded protein in vivo. A second protein under study is that responsible for a specific RNA editing step which occurs in delta mRNA at base 1012, near a region of local tertiary structure similar to that implicated in PKR binding. The editing activity, an RNA-dependent adenosine deaminase, has been isolated from mammalian cells and shown to edit delta mRNA transcripts in vitro with the required specificity in a collaborative study with Dr. T. Maniatis, Harvard University. We are studying a cellular mRNA also known to be edited in vivo by the same enzyme—that for the GluR-B receptor component—in parallel with the delta experiments. RNA:protein binding and protection studies to probe the structure and specificity of the delta and GluR-B RNA recognition sites are under way.

**RECENT PUBLICATIONS**


**Circle, D. A., Neel, O. D., Clarke, P., Mathews, M. B. and Robertson, H. D. Surprising specificity of PKR binding to delta agent genomic RNA. RNA 3:1-11, 1997.**

**Neel, O. D. and Robertson, H. D. Pathways of RNA ligation in the replication of the hepatitis delta agent. Nucleic Acids Symposium Series, No. 36, Oxford Univ. Press, pp. 154-155, 1997.**


*Cell Biology & Genetics*

*Biochemistry & Structural Biology*

# Enriqué Rodriguez-Boulan, M.D.

## RETINAL CELL BIOLOGY AND MACULAR DEGENERATION

A main interest of this laboratory is the interaction between the neural retina (NR) and the retinal pigment epithelium (RPE). This interaction is key for photoreceptor survival and is altered in two major eye diseases that, combined, are the major causes of blindness in the United States . A degenerative disease that affects the elderly, *macular degeneration*, originates in progressive loss of function of RPE, a process related to aging since RPE cells do not renew themselves. *Diabetic retinopathy* is characterized for the excessive growth of new retinal blood vessels which leads eventually to retinal detachment, rapid deterioration of photoreceptors and permanent loss of vision. Medical treatment of these diseases depends on the elucidation of the molecular mechanisms responsible for photoreceptor and RPE cell death. Our laboratory has recently identified key molecules involved in RPE-photoreceptor interaction, including an integrin receptor that plays a essential role in phagocytosis of photoreceptor outer segments and a protein that plays a key role in remodelling of the extracellular matrix. We plan to use the knowledge generated by these studies to devise meaningful therapeutical strategies, including gene therapy.

EPITHELIAL BIOLOGY AND TRANSFORMATION. POLARIZED PROTEIN TRAFFICKING.

Another major research area in the laboratory is the study of the molecular basis of protein sorting in polarized cells. We are currently identifying components of the machinery that sorts proteins in the Trans Golgi Network of epithelial cells and neurons using molecular and biochemical approaches. We also study the role of cell adhesion molecules in the genesis of the epithelial phenotype and how neoplastic transformation leads to loss of the polarized phenotype, an early event in carcinogenesis.

**RECENT PUBLICATIONS**


**Finneman, S., Bonilha, V., Marmorstein, A. and Rodriguez-Boulan, E. Phagocytosis of Rod Outer Segments by Retinal Pigment Epithelium requires avb5 Integrin for Binding but not for Internalization. Proc. Natl. Acad. Sci., USA 94:12932-37, 1997.**

**Marmorstein, A.D., Gan, Y., Finnemann, S., Csaky, K.G., and Rodriguez-Boulan E. Apical Polarity of N-CAM and EMMPRIN in Retinal Pigment Epithelium Resulting from Suppression of Basolateral Signal Recognition. J. Cell Biol. 142: 697-710, 1998.**


*Cell Biology & Genetics*

*Neuroscience*

# Michael K. Rosen, Ph.D.

## STRUCTURAL BASIS OF SIGNAL TRANSDUCTION THROUGH RHO-FAMILY GTPASES

Research in the Rosen laboratory is aimed at deciphering the molecular mechanisms of signal transduction through Rho-family GTPases in the Ras superfamily. The tools used in these studies include protein nuclear magnetic resonance spectroscopy (NMR), biochemistry, molecular biology, and synthetic organic chemistry.

The Rho-family GTPases Rho, Rac and Cdc42Hs, play key roles in organizing the actin cytoskeleton in cells. Thus, they are critically involved in cellular processes such as growth, movement, and the maintenance of shape and polarity. The deregulation of these processes can lead to the characteristic morphological changes observed in tumor cells, and in the increased invasiveness of highly mobile metastatic cells. For this reason, an understanding of Rho-family signaling will contribute both to our basic understanding of cell function, and to the body of knowledge that may ultimately lead to treatments or cures for cancer.

Like all members of the Ras superfamily, Rho, Rac and Cdc42Hs exist in two states. When bound to GTP, the proteins are able to interact with and activate downstream effector molecules, resulting in transmission of a signal. When bound to GDP, interaction with effectors does not occur, and signaling pathways are inactive. Research in the laboratory currently focuses on structural and functional analyses of several proteins that regulate GTPase nucleotide state, as well as several effector molecules. Greatest progress has been made in studies of the negative regulator, RhoGDI. This protein inhibits Rho-family signaling by binding the C-terminal isoprene of the GTPases and consequently extracting them from membranes, and by preventing GTPase cycling between nucleotide states. Through a combination of structural and biochemical studies, we have developed a model of RhoGDI function where a C-terminal binding domain targets an N-terminal inhibitory peptide to GTPases, resulting in membrane extraction and inhibition of nucleotide cycling.

Future studies in this area will explore the regulation of RhoGDI-GTPase complexes by the protein ezrin, which has recently been shown to bind RhoGDI, displacing it from its targets. Interestingly, ezrin also binds to CD44, an extracellular matrix receptor that in variant forms can increase the metastatic potential of certain tumors. Current models suggest that in normal cells ezrin may deposit GTPases proximal to CD44, at regions of the plasma membrane where actin must be polymerized in order to facilitate cell movement. Improper control of this process could contribute to the repeated changes in adhesiveness necessary for metastatic cell growth. Through understanding the molecular details of ezrin's interactions with RhoGDI and with CD44 we hope to gain general insights into mechanisms of cell adhesion and tumor metastasis.

**RECENT PUBLICATIONS**


**Gosser, Y.Q., Nomanbhoy, T.K., Aghazadeh, B., Manor, D., Combs, C., Cerione, R.A., Rosen, M.K. C-terminal binding domain of Rho-GDP dissociation inhibitor directs N-terminal inhibitory peptide to GTPases. Nature 387:814-819, 1997.**


*Biochemistry & Structural Biology*

# Neal Rosen, M.D., Ph.D.

## ACTIVATED TYROSINE KINASE-REGULATED SIGNAL TRANSDUCTION PATHWAYS IN HUMAN SOLID TUMORS

The main goals of our laboratory are the identification and characterization of tyrosine kinase-regulated signal transduction pathways that are necessary for maintenance of transformation in human epithelial tumors and the development of inhibitors of elements of these pathways that can be used as research tools and therapeutic agents.

Human breast and colorectal cancer have been used as model systems in which we have shown that activation of wild type ras by receptor or src-related tyrosine kinases leads to deregulation of the cell cycle and to redifferentiation. Tyrosine kinase inhibitors such as herbimycin A reverse the transformed phenotype and cause G1 arrest and apoptosis. G1 arrest is mediated by loss in cyclin D expression and an induction of expression of the cyclin kinase inhibitor p27.

Current work is directed at delineating the pathways through which tyrosine kinase activation leads to G1 deregulation and in developing drugs that revert transformation by inhibiting such pathways. We have demonstrated that herbimycin A works by altering the interaction of selected target proteins with hsp90 and causing their selective degradation via a ubiquitin and proteasome sensitive pathway. We have shown that farnesyl transferase inhibitors prevent p21ras processing and repress transformation in many human cancers. Investigation of the mechanism(s) that underlie the effects of these two drugs and establishing their potential clinical utility is the other major goal of the laboratory.

**RECENT PUBLICATIONS**


**Sepp-Lorenzino, L., Ma, Z., Lebwohl, D.E., Vinitsky, A., and Rosen, N. Herbimycin A Induces the 20 S proteasome- and ubiquitin-dependent degradation of receptor tyrosine kinases. J. Biol. Chem. 270:18580-18587, 1995.**

**Sepp-Lorenzino, L., Ma, Z., Rands, E., Kohl, N.E., Gibbs, J.B., Oliff, A. and Rosen, N. A peptidomimetic Inhibitor of farnesyl:protein transferase blocks the anchorage-dependent and -independent growth of human tumor cell lines. Cancer Res. 55:5302-5309, 1995.**


*Cell Biology & Genetics*

# Myrna R. Rosenfeld, M.D., Ph.D.

## MOLECULAR NEUROBIOLOGY

Research in this laboratory spans two areas. First, is the development of novel therapies for primary brain tumors with a current focus on the p53 tumor suppressor gene and angiogenesis. The other area is the study of novel tumor antigens associated with neurologic paraneoplastic disorders.

We have demonstrated that 40% of extremely long-term survivors (> 7 years)of glioblastoma multiforme had tumors that overexpressed wild-type p53 protein but none that expressed mutant p53. In another study we demonstrated that 21% of patients with primary glial tumors harbor anti-p53 antibodies; the presence of these antibodies was associated with a longer mean survival. This and other work supports our belief that the p53 gene plays a critical role in these tumors and is a rational target for gene therapy. Secondly, it suggests that p53 may be a suitable candidate for tumor vaccination with the goal of provoking a tumor specific cytotoxic T cell response.

Using defective herpes and adeno-associated viral vectors we found that replacement of the p53 gene results in restoration of tumor suppressor gene function and that our vectors can be used to safely transfer genes to implanted leptomeningeal tumors in vivo. We are currently studying how tumor suppressor gene replacement alters tumor response to chemotherapy and irradiation. Other studies are exploring the use and development of anti-angiogenic agents as potential adjuvant treatments for brain tumors.

Our laboratory is also interested in the cloning and characterization of tumor antigens involved in paraneoplastic neurologic disorders. Patients with these disorders develop immune responses, characterized by high titers of antibodies against antigens whose expression is restricted to the tumor and nervous system. We have used these antibodies to screen cDNA libraries to clone these tumor specific and neuronally restricted proteins (onconeural antigens). Several of these genes have been shown to be important in neuronal development and maintenance.

**RECENT PUBLICATIONS**


**Rosenfeld, M.R., Bergman, I., Schramm, L., Griffin, J.A., Kaplitt, M.G., and Meneses, P.I. Adeno-associated viral vector gene transfer into leptomeningeal xenografts. J Neuro-oncol 34:139-144, 1997.**

**Frennier, J., Abrey, L.E., Haimovitz-Friedman, A., McLoughlin, M., Rosenfeld, M.R. Does thalidomide have a role in glioma angiogenesis? Neurology 50:A383-384, 1998.**


*Neuroscience*

# James E. Rothman, Ph.D.

## CELL BIOLOGY; NEUROBIOLOGY

In cell biology, we are interested in understanding the molecular mechanisms of budding and fusion of transport vesicles. Transport pathways involving vesicles are responsible for the compartmentalization of the cytoplasm and the secretion of proteins. Related processes underlie synaptic transmission.

Building on the reconstitution of vesicle transport, first achieved in 1980, the core machinery for budding vesicles (ARF, GTPases and coat proteins) and docking and fusing them (v-SNAREs, t-SNAREs, SNAPs with ATPase NSF) was identified. We are now focused on understanding I) the mechanism of budding and cargo packaging; ii) the mechanisms of lipid bilayer fusion; and iii) its regulation in synaptic transmission.

In neurobiology, we are developing genetically encodable optical probes that can allow synaptic transmission and, potentially membrane potential to be sensitively and rapidly imaged in populations of neurons in cultures and in brain slices. These technologies can be used to study coherent population behavior such as synchronized oscillations that are poorly addressed by existing electrical and chemical dye-based imaging methods.

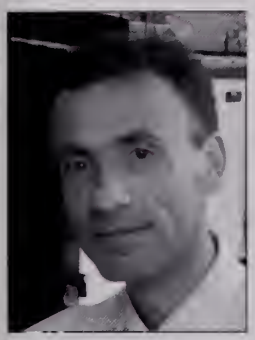
**RECENT PUBLICATIONS**


**Miesenbock, G. and Rothman, J.E. Patterns of synaptic activity in neural networks recorded by light emission from synaptolucins. PNAS 94:3402-3407, 1997.**

**Weber, T., Zemelman, B., McNew, J., Westermann, B., Gmachl, M., Parlati, F., Sollner, T., Rothman, J.E. SNAREpins: Minimal machinery for membrane fusion. Cell 92:1-20, 1998.**


*Biochemistry & Structural Biology*

*Cell Biology & Genetics*



# Carlo Russo, M.D.

## T CELL IMMUNOBIOLOGY OF AGING

The functional consequence of the age-associated changes in the immune system is an increased susceptibility to infectious and autoimmune diseases. The molecular mechanisms underlying these changes remain for the large part still unclear. Dr. Russo's laboratory research interest is the analysis of the T cell repertoire in aging. T cells mature and are selected in the thymus that involutes at an early age; whether T cell maturation occurs later in life and where remain open questions. Dr. Russo's working hypothesis is that the two major age-associated changes in T cell function, that is, increased auto-antibody synthesis and decreased response to foreign antigens, are interconnected and dependent on a structural change of the T cell repertoire. The laboratory goal is to identify these molecular changes and correlate them to the altered immune function observed in elderly humans. It has been observed that with increasing age, there is an increase in humoral and cellular immune autoreactivity. Potentially autoreactive T cells are normally kept in control by the thymus. We have evidence suggesting that the increased presence of autoreactive T cells in elderly subjects may be of extrathymic origin. Monoclonal expansions of nonmalignant B cells occur frequently in old individuals. Clinically, this condition is termed "Benign Monoclonal Gammopathy" (BBMG) and is thought to be a consequence of chronic stimulation of B cells by self-antigens or microbial antigens over a lifetime. We have found what could be the T cell equivalent of BBMG: oligoclonal expansions of CD8+ CD28- cells. The functional role of these expanded CD8+ CD28- clones is not known. The goal of this project is to investigate the activation requirements, antigen-specificity and biological significance of these clonal expansions of T cells in inflammatory and autoimmune disorders.

Alterations in T cell function may play a role in the increased morbidity and mortality during outbreaks of influenza in elderly subjects. Although annual influenza vaccination is strongly recommended for administration to all persons 65 and older, the vaccine's effectiveness has been a subject of great debate. We have recently reported that between 40 and 50% of healthy, community residing elderly individuals vaccinated do not develop immunity to the vaccine and therefore, remained susceptible to influenza infection. We have obtained evidence that T cells from subjects who did not develop a protective antibody titer fail to respond in vitro to the influenza vaccine. The goal of these studies is to identify defects in the immune response of elderly humans to foreign antigens. These studies ultimately will allow us to define better strategies for vaccination of elderly subjects against viral infections and to prevent the development of self-reactivity.

**RECENT PUBLICATIONS**


**Gross, A. P., Russo, C., Dran, S., Cataruozolo, P., Munk, G., and Lancey, S.C. Time to earliest peak serum antibody response to influenza vaccine. Clin. & Diagn. Lab. Immunol. 4:491-492, 1997.**

**Nociari, M., Shalev, A., Benias, P., and Russo, C. A novel one-step, highly sensitive fluorometric assay to evaluate cell-mediated cytotoxicity. J. Immunol. Meth. (In Press), 1998.**


*Immunology*

# Urs Rutishauser, Ph.D.

## CELLULAR AND DEVELOPMENTAL NEUROBIOLOGY

Our group investigates cell-cell interactions during development, with a primary focus on the nervous system. The key question being addressed is how cell interactions are regulated at the cellular level in order to create changes in cell morphology and tissue structure.

These investigations are largely based on our findings that the polysialic acid (PSA) moiety of the neural cell adhesion molecule (NCAM) can serve as a global regulator of cell interactions. In particular, we are analyzing events "upstream" of PSA expression, such as morphogenetic programs and synaptic activity, and "downstream" effects of PSA, such as the promotion of cell migration, axon guidance, and synaptic remodeling.

At the molecular level recent advances have been the identification of a specific recognition site on NCAM for addition of PSA, evidence that PSA expression can be controlled by intracellular pools of calcium, and the design of biophysical tools to elucidate the mechanism of PSA action at the cell surface. At the physiological level, this mode of regulation has been found to affect not only development, but also adult CNS plasticity, as evidence by effects on circadian rhythms generated in the suprachiasmatic nucleus and learning/memory models associated with the hippocampus.

This work requires a very broad range of research disciplines at the gene, protein, cell and tissue level, and includes gene targeting, transgenic mice, molecular biological analysis of protein domains, elucidation of intracellular signaling pathways, membrane biochemistry and biophysics, and a variety of anatomical and physiological analyses in the developing and adult nervous system.

**RECENT PUBLICATIONS**


**Hu, H., Tomasiewics, H. Magnuson, T. and Rutishauser, U. The role of polysialic acid in migration of olfactory bulb interneuron precursors in the subventricular zone. Neuron 16, 735-743, 1996.**

**Bruses, J. L., and Rutishauser, U. Regulation of NCAM polysialylation: evidence for nontranscriptional control and sensitivity to an intracellular pool of calcium. J. Cell Biol. 140:1177-1186, 1998.**


*Cell Biology & Genetics*

# Timothy Ryan, Ph.D.

## SYNAPTIC PHYSIOLOGY, NEUROBIOLOGY, MEMBRANE TRAFFIC, OPTICAL MICROSCOPY

The central focus of the laboratory is the study of synaptic communication between neurons of the CNS. We rely heavily on the development and use of new optical microscopy and biophysical techniques to study the properties of synapses in living cells. Generally, the research focuses on the central question of determining how synaptic efficacy is modulated in the brain. Our approach is to study synaptic connections in vitro, formed between rat or mouse neurons grown in cell culture, where they are most amenable to detailed cell biological, physiological, molecular and biophysical investigation. By determining both the cellular processes and their molecular substrates that underlie synaptic function we hope to gain insight into how information is controlled at the synaptic level in both normal and diseased states of brain function.

We make use of fluorescent probes of membrane traffic at synapses to perform quantitative measures of presynaptic function. Using the fluorescent membrane marker FM 1-43 we can both identify viable synapses in living cells as well as characterize the detailed kinetics of various branches of vesicle recycling: exocytosis, endocytosis and vesicle repriming. This methodology provides a powerful approach for studying the physiology of synaptic function at the single synapse level and has recently been extended to achieve sensitivities at the level of single quanta. The molecular basis of synaptic function is being explored using transgenic mice lacking key synaptic constituents as well as wild type neurons bearing altered synaptic proteins introduced via viral transfection.

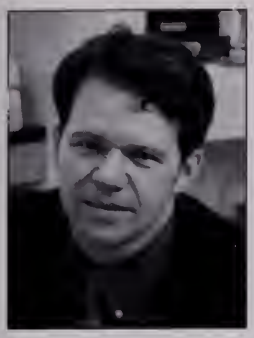
**RECENT PUBLICATIONS**


**Ryan, T.A., Li, L., Chin, L-S., Greengard, P. and Smith, S.J. Synaptic vesicle recycling in synapsin I knockout mice. J. Cell Biol. 5:1219-1228, 1996.**

**Ryan, T.A., Reuter, H. and Smith, S.J. Optical detection of quantal presynaptic membrane turnover. Nature 388:478-482, 1997.**


*Biochemistry & Structural Biology*

*Neuroscience*



# Michel Sadelain, M.D., Ph.D.

## GENE TRANSFER AND GENE EXPRESSION

***Research Interests:*** Genetic approaches to enhance immune responses: control of transgene expression; medical applications of retroviral-mediated gene transfer.

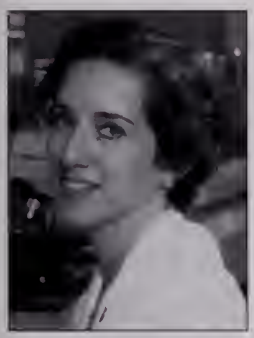
***Description of Research:*** The safe and efficient transfer of genes into human primary cells provides the basis for novel and powerful approaches to the study, prevention, and treatment of disease. This laboratory is dedicated to improving gene transfer and gene expression in cells of hematopoietic origin, and to utilize retroviral-mediated gene transfer to treat genetic disorders and cancer. ***Genetic control of immune responses in vivo***– Recently we established efficient methods for gene transfer in murine and human primary T lymphocytes, which opens up new venues for the study of lymphocyte biology as well as the manipulation of T lymphocytes for therapeutic purposes. Our efforts are centered on the therapeutic use of T lymphocytes in the context of graft-versus-host disease (GVHD), graft-versus-leukemia, and solid tumors. We are currently investigating how to enhance the cytotoxic activity of T cells against tumor cells and the survival of adoptively transferred T cells. As part of a multi-laboratory effort, we are also investigating the therapeutic potential of genetically modified bone marrow-derived dendritic cells. These professional antigen-presenting cells are uniquely poised to process and present antigens, especially the self-antigens typically overexpressed by transformed cells. ***How to achieve tissue-specific and position-independent gene expression in hematopoietic cells***– Recombinant retroviruses integrate in the target cell genome and thus are transmitted to the target cell's progeny, a key feature for stably altering cells undergoing clonal expansion, such as T lymphocytes and hematopoietic stem cells. However, integration at random chromosomal sites exposes the transgene to the repressive influence of flanking chromatin which can lead to dysregulated transgene expression or transcriptional silencing. We are investigating how to overcome variegated expression of randomly integrated retroviral vectors. For this purpose, we take advantage of the globin gene model, focusing on the transcriptional requirements for tissue-specific and position-independent expression of a retrovirally encoded -globin gene.

**RECENT PUBLICATIONS**


**Gallardo, H. F., Tan, C., Ory, D., Sadelain, M. Recombinant retroviruses pseudotyped with the vesicular stomatitis virus G glycoprotein mediate both stable gene transfer and pseudotransduction in human peripheral blood lymphocytes. Blood 90: 952-957, 1997.**

**Gallardo, H.F., Tan, C., Sadelain, M. The internal ribosomal entry site of encephalomyocarditis virus enables very reliable coexpression of two transgenes in human primary T lymphocytes. Gene Therapy 4: 1115-1119, 1997.**


*Immunology*



# Jane E. Salmon, M.D.

## HUMAN PHAGOCYTE BIOLOGY

The primary investigative interests of this laboratory are the study of human receptors for immunoglobulin (Fc receptors) and their polymorphisms. Different receptor isoforms and polymorphic forms have distinct functional capacities with clear contributions to host defenses and to the pathogenesis of autoimmune disease. Several critical observations underscore the important role of Fcγ receptors: (1) FcγR are essential to the inflammatory response in animal models of immune complex disease; (2) Fcγ dependent phagocyte function is abnormal in human immune complex disease (systemic lupus erythematosus is the classic example); (3) FcγR allelic forms are abnormally distributed in human autoimmune diseases. These observations, coupled with emerging knowledge about the diversity in receptor structure and function, focus attention on several critical questions.

***Signal transduction of FcγR isoforms.*** Different receptor isoforms have distinct functional capacities as evidenced both by the proximal signaling elements engaged and by the cell programs elicited. Such differences provide the basis for the unique contributions of allelic forms to host defenses and to autoimmunity. Early tyrosine phosphorylation is a common theme, and studies are underway to define the different signaling pathways engaged by each receptor type and their regulation by other receptor systems. Such studies will provide important approaches to the understanding and therapeutic manipulation of the diverse biologic responses elicited by IgG ligand.

***Allelic polymorphisms and receptor function.*** Allelic variants of Fcγ receptor isoforms can strongly influence receptor function. The R131/H131 variants of FcγRIIA alter the ability of the receptor to bind human IgG2 and impact on the risk of serious infection by encapsulated bacteria and of renal disease in systemic lupus erythematosus. Allelic variants of FcγRIIIB determine risk of severe kidney damage in vasculitis. Studies are now underway to define the basis for these differences and to identify new and physiologically significant polymorphic forms affecting the function of immune effector systems.

**RECENT PUBLICATIONS**


**Salmon, J.E., Millard, S. S., Brogle, N., Kimberly, R.P. Fcγ receptor IIIb enhances FcγRIIa function in an oxidant-dependent and allele-sensitive manner. J Clin. Invest. 95:2877-2885, 1995.**

**Salmon, J.E., Millard, S., Schacter, L.A., Arnett, F.C., Ginzler, E.M., Gourley, M.F., Ramsey-Goldman, R., Kimberly, R.P. FcγRIIA alleles are heritable risk factors for lupus nephritis in African-Americans. J Clin. Invest. 97:1348-1354, 1996.**


*Immunology*

# Derek B. Sant'Angelo, Ph.D.

## THE IMMUNOBIOLOGY OF T CELLS

The primary requirement for the intrathymic development of αβ T cells to maturity is an appropriate interaction of the T cell receptor (TCR) with a self-peptide:MHC complex. This interaction mediates the complex processes of positive and negative selection. Thymocytes bearing useful TCR receive a positive selection signal that allows these cells to survive and differentiate whereas cells bearing potentially self-reactive TCR die after receiving a negative signal. My laboratory focuses on this delicate receptor/ligand interaction as well as the biological consequences of this interaction.

Using TCR β chain transgenic mice, we have developed a unique approach which allows us to compare the TCR repertoire before and after positive selection. Using this approach we have been able to directly assess the impact that intrathymic self-peptides have on the diversity of the mature TCR repertoire. These studies are now being extended to examine how alterations of the intrathymic peptide repertoire affect the specificity of the mature TCR repertoire. To do this the antigen processing machinery of the cortical epithelial cells that support positive selection will be manipulated by introducing various transgenes. One aspect of this work will be to study the link between certain MHC class II alleles and autoimmune diseases such as diabetes and multiple sclerosis.

Analysis of TCR β chain transgenic mice has also allowed us to define one of the earliest intrathymic populations of cells that has been positively selected. These cells, which are characterized by the expression of cell surface markers ($CD4^+CD8^+TCR^{lo}$ enlarged cells), can be further divided into two novel populations. The developmental potential of these two populations is now being studied. By a molecular analysis of the first positively selected subpopulation as compared to its immediate precursor, we anticipate being able to identify genes that play a role in this selection process. Determining what genes are involved is a critical aspect of understanding how the positive selection event is mediated.

**RECENT PUBLICATIONS**


**Sant'Angelo, D.B., Waterbury, P.G., Cohen, B.E., Martin, W.D., Van Kaer, L., Hayday, A. C. , and Janeway, C.A. The imprint of self peptides on the mature T cell receptor repertoire. Immunity 7:517-524, 1997.**

**Sant'Angelo, D.B., Lucas, B., Waterbury, P.G., Cohen, B., Brabb, T., Goverman, J., Germain, R.N., and Janeway, C.A. A molecular map of T cell development. Immunity, 1998, In press.**


*Immunology*

# Elaine Schattner, M.D.

## IMMUNE BIOLOGY OF LYMPHOCYTIC TUMORS

The research focus of my laboratory is proliferation and apoptosis of normal and malignant B lymphocytes. One major project centers on the Fas receptor (CD95), which can transmit a death signal to cells such that they undergo apoptosis. We have identified that CD40 ligation in germinal center B cells by the ligand on T cells (CD40L, CD154) induces CD95 upregulation. In the absence of inhibitors to apoptosis, ligation of CD95 triggers a cascade of signaling events resulting in caspase activation and cell death. We have reported that this is an important mechanism by which CD4+ T cells regulate the growth of certain B cell tumors, such as Burkitt's lymphoma. The aims of the work now are to define mechanisms of resistance to Fas-mediated apoptosis in B cells, such as that induced by crosslinking of the surface antigen receptor, or by intracellular viral gene products. We are evaluating how this system for inducing cell death can be applied to other B cell malignancies, and are using a murine model to test application of this signaling pathway in vivo. The second major project regards immune regulation in chronic lymphocytic leukemia (CLL). We have reported that CD154 is aberrantly expressed in some CLL tumor B cells and may be a factor in the generation of pathogenic autoantibodies, and have determined that CLL B cells have high levels of the transcriptional regulator NF B, which can be modulated by specific immunologic signals. The goals are to characterize NF B in CLL and to evaluate how NF B activity can be modified to facilitate CLL B cell death. Through these investigations, we hope to apply advances in our understanding of normal immune regulation of T and B lymphocytes to develop novel strategies for control of human lymphocytic leukemias and lymphomas.

**RECENT PUBLICATIONS**


**Schattner, E.J., Mascarenhas, J., Reyfman, I., Koshy, M., Woo, C., Friedman, S.M., Crow, M.K. Chronic lymphocytic leukemia B cells can express CD40 ligand and demonstrate T-cell type costimulatory capacity. Blood 91:2689-2697, 1998.**

**Bishop, J., Schattner, E.J., Friedman, S.M. CD40 ligation impedes lymphoblastoid B cell proliferation and S-phase entry. Leukemia Research 22; in press (1998).**


*Immunology*

# David A. Scheinberg, M.D., Ph.D.

## HEMATOPOIETIC CANCER IMMUNOCHEMISTRY

We study the mechanisms of action and the therapeutic applications of immunotherapy for hematopoietic cancers. There are two general areas of investigation: Specific monoclonal antibody therapies of leukemias and lymphomas and active specific immunotherapies (vaccines) for leukemias. The work in the laboratory ranges from basic investigation into the biochemistry and immunochemistry of antibody and vaccine action to clinical application of developed products.

One project focuses on the development of alpha particle emitting monoclonal antibody constructs. Alpha particles have the advantage of extremely high potency single cell killing with limited bystander cell killing. The chemistry of the production of pure alpha emitting radionuclides and their stable attachment to specific monoclonal antibodies as well as their use *in vitro* and in animal models is under investigation. Clinical trials are underway. Another project focuses on the mechanisms of resistance of tumor cells to antibody based therapies. MDR-1 (P-glycoprotein) appears to play a role in resistance to complement mediated cytotoxicity, but not to antibody dependent cellular cytotoxicity mediated by NK cells. We are investigating other mechanisms of action of resistance to immunotherapy.

As most human leukemias are associated with non-random chromosomal translocations, of which many produce novel fusion proteins as a product of the fusion gene, this provides a tumor specific target for active specific immunotherapy. The laboratory is investigating the binding of peptides derived from the fusion proteins to MHC molecules, which is a necessary prerequisite for recognition of the antigen by cytolytic T cells and helper T cells. *In vitro* models of specific T cell cytolysis and proliferation against these tumor specific peptides are also under investigation. These investigations have led to a vaccine for CML which is being studied in human clinical trials. Extension of this work into other leukemias and other diseases where specific peptide sequences are available is underway.

**RECENT PUBLICATIONS**


**Weisburg, J.H., Curcio, M, Caron, P.C., Raghu, G., Mechetner, E,, Roepe, P.D., and Scheinberg, D.A., The multidrug resistance (MDR) phenotype confers immunological resistance. J. Exp. Med. 183:2699-2705, 1996.**

**Bocchia, M., Korontsvit, T., Xu, Q., Mackinnon, S., Yang, S.Y., Sette, A., and Scheinberg, D.A. Specific human cellular immunity to bcr-abl oncogene-derived peptides. Blood 87:3587-3592, 1996.**


*Pharmacology*

# Beate Schwer, Ph.D.

## PRE-mRNA PROCESSING

The precise removal of intervening sequences from primary transcripts by splicing is an essential step in the production of functional messenger RNA in every eukaryotic cell. Our goal is to understand the mechanisms of pre-mRNA splicing and the molecular interactions involved. Our studies employ the powerful techniques available in the yeast *S. cerevisiae*. The immediate objectives are: (1) to identify and characterize splicing factors and (2) to elucidate critical protein/RNA and protein/protein interactions within the splicing complex (spliceosome). We are particularly interested in understanding how RNA-dependent ATPases and RNA helicases, such as Prp16 and Prp22, affect conformational rearrangements in the spliceosome, essential to drive the splicing reaction forward and to ensure fidelity.

Our studies focus on the second step of splicing; this step encompasses the recognition of the 3' splice site and the joining of the exons. We have developed assay systems to halt the reaction at various distinct stages during step 2; activity can be restored by the addition of purified components. Our studies demonstrated that in response to ATP hydrolysis by Prp16, several protein factors (i.e. Slu7, Prp22, Ssf1) enter the spliceosome. They play roles in the selection of the 3' splice site and are essential for the formation of mature mRNA.

The biochemical characterization of second step factors is complemented by genetic approaches. These take advantage of our collection of mutants in individual components; genetic interactions identify likely physical and functional connections not only between splicing factors, but also between splicing factors and components of other pre-mRNA processing machineries.

**RECENT PUBLICATIONS**


**Zhang, X.P. and Schwer, B. Functional and physical interaction between the yeast splicing factors Slu7 and Prp18. Nucleic Acids Res. 25:2146-2152, 1997.**

**Schwer, B. and Gross, C.H. Prp22, a DExH box RNA helicase, plays two distinct roles in yeast pre-mRNA splicing. EMBO J. 17:2086-2094, 1998.**


*Molecular Biology*

# Kathleen W. Scotto, Ph.D.

## TRANSCRIPTIONAL REGULATION OF DRUG RESISTANCE GENES

Drug resistance is a major barrier to successful chemotherapy. The emergence of resistance in a tumor population is most often associated with a disregulation of gene expression, usually at the level of transcription. One of the major goals in the field of cancer chemotherapy is to define the mechanisms underlying transcriptional regulation of drug resistance genes in an effort to identify targets for therapeutic intervention.

The research in our laboratory has focused on identifying the molecular mechanisms involved in the transcriptional regulation of the P-glycoprotein (Pgp) gene. When overexpressed in tumor cells, Pgp confers resistance to a variety of chemotherapeutic agents; this resistance has been termed MDR (multidrug resistance). Moreover, Pgp is a normal component of a variety of highly differentiated cell types. Therefore, we have investigated the transcriptional regulation of Pgp in both normal tissues and MDR tumor cells. Within the past few years, we have defined several transcription elements/factors that are involved in regulation of Pgp transcription. One novel element, MED-1, is involved in activation of the Pgp promoter in MDR cells, but not in normal drug-sensitive cells. Interestingly, we found that this element and its cognate binding factors are also involved in transcription start site selection; we are now addressing fundamental questions regarding the interaction of this DNA/protein complex with the basal transcription machinery. We have also determined that steroid hormones repress Pgp transcription through an activator occlusion mechanism; we are presently investigating the molecular interactions between steroid hormones and other transcription factors, and have begun in vivo studies to determine whether steroid hormones can be used as adjuvants for the treatment of MDR tumors. Our most recent findings have led us to the study of chromatin-mediated regulation of transcription. We have determined that Pgp transcription is regulated by histone acetylase/deacetylases, and have identified a specific DNA element and transcription factor which mediate this regulation; we are presently defining the signal transduction events that modulate the activity of this element/factor.

**RECENT PUBLICATIONS**


**Ince, T.A. and Scotto, K.W. A conserved downstream element defines a new class of RNA polymerase II promoters J. Biol. Chem. 270:30249-30252, 1995.**

**Jin, S. and Scotto, K.W. Transcriptional regulation of the MDR1 gene by histone acetylases/deacetylases is mediated by NF-Y. Mol. Cell Biol. (in press), 1998.**


*Pharmacology*

# Stewart Shuman, M.D., Ph.D.

## RNA CAPS AND DNA TWISTS

mRNA processing occurs cotranscriptionally as nascent chains are being synthesized by RNA polymerase. The earliest modification is the formation of the 5' m7GpppN cap. Capping occurs by a series of three enzymatic reactions in which the 5' triphosphate terminus of a primary transcript is first cleaved to a diphosphate by RNA triphosphatase, then capped with GMP by RNA guanylyltransferase, and methylated at the N7 position of guanine by RNA (guanine-7) methyltransferase. The catalytic activities of these three enzymes are essential for cell growth. We are studying the mechanism of cap synthesis and the role of the cap in mRNA metabolism. We are focusing on the following questions. What structural features are essential for the triphosphatase, guanylyltransferase, methyltransferase activities? To what extent are these features conserved? How do the essential structural elements illuminate the reaction mechanisms? How is the capping apparatus targeted in vivo to modify only pre-mRNAs? What happens to cellular physiology when the cap-forming enzymes are genetically inactivated?

Eukaryotic type I topoisomerases relax DNA supercoils that arise during replication and transcription. The reaction involves formation of a covalent DNA-(3'-phosphotyrosyl)-protein intermediate. We are studying the structure and mechanism of topo I using the vaccinia enzyme as a model. Through mutational analysis, we've identified a constellation of 5 amino acids that catalyzes attack of the tyrosine on the scissile phosphate. The structure of the catalytic domain of vaccinia topo (solved by X-ray crystallography) resembles the catalytic domains of site-specific recombinases that act via a topo I-like mechanism. The topoisomerase catalytic pentad is conserved in the tertiary structures of the recombinases, despite scant sequence similarity overall. This implies that the catalytic domains of type IB topoisomerases and recombinases derive from a common ancestral strand transferase. We are now examining the role of topo I as a catalyst of recombination *in vivo* and *in vitro*.

**RECENT PUBLICATIONS**


**Hakansson, K., Doherty, A. J., Shuman, S., and Wigley, D. B. X-ray crystallography reveals a large conformational change during guanyl transfer by mRNA capping enzymes. Cell 89:545-553, 1997.**

**Cheng, C., Kussie, P., Pavletich, N., and Shuman, S. Conservation of structure and mechanism between eukaryotic topoisomerase I and site-specific recombinases. Cell 92:841-850, 1998.**


*Molecular Biology*

*Biochemistry & Structural Biology*

# Randi B. Silver, Ph.D.

## INTRACELLULAR PH AND CA2+ REGULATION AND SIGNALLING PATHWAYS

Intracellular $Ca^{2+}$ and pH both play extremely important roles in cellular homestasis. The primary focus of our laboratory is studying intracellular pH regulation and variations in cystolic $Ca^{2+}$ levels as they relate to pertubations in either acid-base state or fluctuations in ion transport in renal tubules and renal-related cell lines. Much of this work is performed in the cells of the cortical collecting of the mammalian nephron, which is primarily responsible for both acid-base regulation and $Na^+$ and $K^+$ balance. The interactions of intracellular $Ca^{2+}$ and pH as they relate to epithelial cell functions are being studied using dual wavelength fluorescent pH and $Ca^{2+}$ indicators. These indicator molecules are loaded intracellularly and monitored by ratiometric digital imaging techniques. When excited by appropriate wavelengths of light, indicators fluoresce to reveal the amount of ions bound to the dye.

These extremely powerful tools allow us to view dynamic changes in intracellular pH and $Ca^{2+}$ at the cytoplasmic level without disruption of cell function. Most recently we have applied these techniques in investigating the functional activity of an ATPase that is responsible for $H^+$ and $K^+$ balance in the cortical collecting tubule. We will next apply fluorescence biotechnology to look at the role of intracellular ions at the level of cell function as it relates to cell structure.

**RECENT PUBLICATIONS**


**Constantinescu, A., Silver, R.B., and L.Satlin. H-K ATPase activity in PNA-binding intercalated cells of newborn rabbit cortical collecting duct. Am. J. Physiol. 272:F167-177, 1997.**

**Silver, R.B., Frindt, G., Mennitt, P., and L. Satlin. (1997) Characterization and regulation of H-K ATPase in intercalated cells of rabbit cortical collecting duct. Journal of Experimental Zoology. 279:443-455.**

**Silver, R.B., Choe, H., and G. Frindt. Low NaCl diet increases H-K ATPase in intercalated cells from rat cortical collecting duct. In press. Am. J. Physiol.**


*Physiology, Biophysics & Molecular Medicine*

# Roy L. Silverstein, M.D.

## CELL ADHESION MOLECULES IN VASCULAR BIOLOGY

The focus of this laboratory is the molecular pathogenesis of thrombosis, atherosclerosis, and inflammation. We are actively studying cellular phagocytic and adhesion receptors and are particularly interested in how cells regulate expression of these molecules and in the mechanisms by which they transmit cellular transmembrane signals. Studies include:

1. Molecular and cellular biology of a cell surface protein known as CD36. Although this was originally described as an adhesion receptor, we now know that CD36 also functions to regulate angiogenesis and as a unique "scavenger receptor" on macrophages and retinal epithelia where it mediates binding and uptake of oxidized LDL, apoptotic cells, and photoreceptor outer segments. We are studying structure-function relationships of CD36, the mechanisms by which CD36 transmits signals, and have generated a CD36 null mouse to study its role *in vivo*.

2. Characterization of monocyte activation induced by adhesion to cytokine-activated endothelial cells. We found that a specific genetic program involving expression of inflammatory cytokines, procoagulants, and scavenger receptors is induced by adhesion of monocytes to E-selectin expressed on the surface of activated endothelial cells. This is a receptor-mediated event that has important implications in the pathogenesis of atherosclerosis and inflammation. Our goals are to define the receptors and ligands that mediate this phenomenon and to dissect the molecular mechanisms by which adhesion induces specific gene transcription.

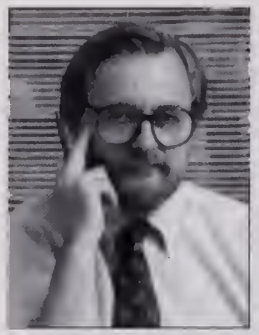
3. Characterization of novel mechanisms of endothelial cell activation. We have shown previously that herpes virus infection can activate endothelial cells to a prothrombotic, proadhesive phenotype. Recent studies have shown that anti-phospholipid autoantibodies (aPL) isolated from patients with the clinical "aPL syndrome" also activate endothelial cells. Current studies focus on the molecular mechanisms by which aPL antibodies interact with and activate endothelial cells.

**RECENT PUBLICATIONS**


**Dawson, D.W., Pearce, S.F.A., Zhong R., Silverstein, R.L., Frazier, W.A., and N.P. Bouck. CD36 mediates the inhibitory effects of thrombospondin-1 on endothelial cells. J. Cell Biology 138:707-717, 1997.**

**Crombie, A.R. and R.L. Silverstein. Lysosomal integral membrane protein II binds thrombospondin1: Evidence of functional homology with the cell adhesion molecule CD36. J. Biol. Chem. 273:4855-4864, 1998.**


*Cell Biology & Genetics*



# Francis M. Sirotnak, Ph.D.

## MOLECULAR THERAPEUTICS

The research of this laboratory focuses on genes regulating expression of molecular targets and other biochemical determinants important to selective antitumor action of various categories of cytotoxic antimetabolites, cytoplasmic membrane transport of pharmacologic agents, molecular mechanisms of acquired resistance of tumor cells to antineoplastic agents, and the regulation of folate and nucleoside transporter gene expression.

Folates play a crucial role in the biosynthesis of macromolecules. Access of tumor cells to exogenous plasma folates is made possible by the existence in the cytoplasmic membrane of a specific high-affinity transport system. Using cDNA probes, the genetic regulation and molecular genetics of this system are now being examined in models which constitutively overproduce or underproduce the transport protein and during induction of tumor cells to terminal maturation. The organization and structure of this gene and its mRNA splicing and the characteristics of the promoters regulating its transcription are also under study.

Folate and nucleoside analogs effectively accumulate in tumor cells via plasma membrane systems normally transporting natural folates and nucleosides. To understand the selective antitumor action of folate and nucleoside analogs, studies are being conducted of the properties and multiplicity of their cellular membrane transport, their interaction with enzyme and macromolecular targets, their intracellular metabolic disposition, and their pharmacokinetics behavior. Mechanisms of acquired resistance in tumor cells to these anitmetabolites and other cytotoxic agents are also studied at the level of their cellular membrane transport and intracellular metabolic disposition. Of special emphasis are our studies on the folate polyglutamylation enzyme, folylpolyglutamyl synthetase, which include studies of the regulation of its gene expression with appropriate molecular probes. The structure of this gene is also under study as well as its promoters which regulate its transcription and tissue specific mRNA splicing.

**RECENT PUBLICATIONS**


**Roy, K., Egan, M.G., Sirlin, S., and Sirotnak, F.M. Posttranscripionally mediated decreases in folylpolyglutamate synthetase gene expression in some folate analogue-resistant variants of the L1210 cell. J. Biol. Chem. 272:6903-6908, 1997.**

**Roy, K., Tolner, B., Chiao, J.H., and Sirotnak, F.M. A single amino acid difference within the folate transporter encoded by the murine RFC-1 gene selectively alters its interaction with folate analogues. J. Biol. Chem. 273:2526-2531, 1998.**


*Pharmacology*

# Gerard P. Smith, M.D.

Areas of interest:

monoamines and peptides in the control of food intake in preweanling and adult rats.

1) Gut peptides released by ingested food serves as negative feedback, satiating signals to terminate eating. We are currently concerned with Cholecystokinin and are investigating the site(s) of its receptor action, its effect on vagal afferent fibers, and the processing of its message by the hindbrain.

2) We are also studying the role of central dopaminergic mechanisms to maintain eating once it is initiated and central serotonin mechanisms to terminate eating in adult and preweanling rats.

**RECENT PUBLICATIONS**


**K. Joyner, G.P. Smith and J. Gibbs. Abdominal and vagotomy decreases the satiating potency of CCK-8 in sham and real feeding. Am. J. Physiol. 264: R916, 1993.**

**E.S. Corp, J. McQuade, T.H. Moran and G.P. Smith. Characterization of type A and type B CCK receptor binding sites in rat vagus nerve. Brain Res. 623: 161-166, 1993.**


*Neuroscience*

# Kendall A. Smith, M.D.

## CYTOKINE REGULATION OF THE IMMUNE RESPONSE

Cytokines are responsible for regulating the activities of the cells that mediate immune/inflammatory reactions. This laboratory is focused on one of the first cytokines to be described, interleukin 2 (IL-2). IL-2 is a 15 kDa protein secreted by antigen-activated T cells that promotes the proliferation and enhances the secretory capacities of all of the major types of lymphocytes, including T cells, B cells and natural killer (NK) cells. The IL-2 stimulated clonal expansion of antigen-selected T cell and B cell clones determines the tempo and magnitude of antigen-specific immune responses, and forms the cellular basis of immunologic memory. To determine the molecular pathways that promote cell cycle progression, methods have been developed to clone immediate/early IL-2 induced genes. Thus far, 6 novel genes have been identified. We are characterizing these genes as to the regulation of their expression by IL-2 receptor activation, and the gene products are being analyzed for their role in promoting T cell proliferation and/or differentiation. Our clinical research projects are centered on developing cytokines, in particular IL-2, as immune stimulants for the treatment of infectious diseases, immunodeficiency diseases, and cancer. In a dose escalation study just completed, we have determined an ultralow dose of IL-2 that can be administered continuously for 6 months without toxicity, that results in a progressive accumulation of circulating NK cells, monocytes and CD4+ T cells in asymptomatic HIV+ individuals. Future trials will focus on combining IL-2 immunotherapy with antiviral chemotherapy.

**RECENT PUBLICATIONS**


**Smith, K.A. Cell Growth Signal Transduction Is Quantal. Annals of the New York Academy of Sciences 766: 263-271, 1995.**

**Jacobson, E.L., Pilaro, F., and Smith, K.A. Rational interleukin 2 therapy for HIV positive individuals: daily low doses enhance immune function without toxicity. Proc. Natl. Acad. Sci. USA 93:10405-10410, 1996.**


*Immunology*

# Thomas Söllner, Ph.D.

## MEMBRANE TRAFFICKING

Eukaryotic cells maintain their unique compartmental organization despite a constant protein and lipid flow between intracellular organelles and the plasma membrane. Thus membranes must pair and fuse in a selective manner. The core machinery mediating these events employs SNARE proteins, a family of compartmentally-specific integral membrane proteins. Since SNAREs are expected to define the functional borders of organelles, we have developed methods to isolate SNAREs from different organelles within mammalian cells. Several novel ptative SNAREs have been identified and are currently being characterized by means of a variety of invitro assays (employing antibodies and deletion constructs) and by localization studies at the EM level. This work should help to reveal vesicular flow patterns, including anterograde and retrograde transport, and to define tin more detail the functional borders of intracellular organelles.

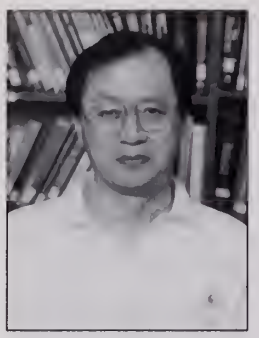
In addition to this core machinery, regulatory proteins are required to restrain or activate SNARE proteins and to ensure localized vesicle docking. A model system for the study of these events is the neuronal synapse. At a highly specialized region, called the "active zone", synaptic vesicles dock and neurotransmitters are released in a quantal manner within a fraction of a millisecond. The active zone is morphologically well defined, but the proteins responsible for forming this specialized structure are unknown. Therefore, major efforts will be made to isolate these active zones in order to reveal the relationship between their structure and function. The identification of the molecular machinery that comprises the active zone should provide insights into mechanisms such as the precise regulation of neurotransmission, synaptogenesis, and possibly learning and memory.

**RECENT PUBLICATIONS**


**Söllner, T., Whiteheart, S.W., Brunner, M., Erdjument-Bromage, H., Geromanos, S., Tempst, P. and Rothman, J.E. SNAP receptors implicated in vesicle targeting and fusion. Nature 362:318-324, 1993.**

**Weber, T., Zemelman, B.V., McNew, J.A., Westermann, B., Gmachl, M., Parlati, F., Söllner, T. and Rothman, J.E. SNAREpins: minimal machinery for membrane fusion. Cell 92:759-772, 1998.**


*Cell Biology & Genetics*



# Jin H. Son, Ph.D.

## MOLECULAR MECHANISMS OF NEUROTROPHIC REGULATION AND CELL DEATH OF BRAIN DOPAMINERGIC NEURONS

Elucidation of the molecular mechanisms by which neurons survive and degenerate at normal and pathophysiological conditions is the major focus of research in our laboratory group. Our model human disease to address the molecular mechanisms of neuronal survival and cell death is Parkinson's disease (PD), of which neuropathological hallmark is the selective degeneration of nigral dopaminergic neurons. Although the initial cause and subsequent signaling mechanisms leading to the dopaminergic cell death underlying the PD remain elusive, the potent neurotrophic factors, BDNF and GDNF, are known to exert neuroprotection against dopaminergic cell death in both animal and cell culture models of PD. To decipher the molecular signaling mechanisms of the neuroprotective role of BDNF and GDNF as well as the cell death caused by oxidative stress and inflammation in dopaminergic neurons, we have developed both in vitro and in vivo model systems: i) a conditionally immortalized dopaminergic precursor neuronal cell line and ii) transgenic animals in which the overexpression of a neurotrophin can be induced by an Tet-on-off genetic switch, without surgical intervention. Using these complementary model systems, we are looking for new therapeutic molecular targets and molecular rationale to slow neuronal cell death in PD.

**RECENT PUBLICATIONS**


**Son, J., Min, N. and Joh, T. Early ontogeny of catecholaminergic cell lineage in brain and peripheral neurons monitored by TH-lacZ transgene. Mol. Brain Res. 36: 300-308, 1996.**

**Son, J. and Joh, T. Genetically engineered neural transmission. Molecular Psychiatry 2: 26-31, 1997.**


*Neuroscience*

# Lisa Staiano-Coico, Ph.D.

## EPITHELIAL DIFFERENTIATION AND WOUND REPAIR

My laboratory has centered on basic and clinical aspects of epidermal biology. We have focused on defining the role of epidermal plasminogen activator inhibitor type-1 (PAI-1), a regulator of matrix integrity and cell-to-matrix adhesion, in directed migration of normal human keratinocytes (NHKs) following wounding and during regenerative maturation. Molecular mechanisms underlying PAI-1 expression were examined in the context of: a) kinetically and immunochemically distinct subpopulations of basal NHKs; and by b) cytoarchitectural reprogramming necessary for NHK migration and differentiation. During regenerative maturation, PAI-1 is confined to particular subpopulations of distinct epidermal cells, is upregulated via a secondary response pathway and that this induction is growth factor and substrate-dependent. PAI-1 induction and NHK differentiation are substrate dependent. Our studies would suggest that growth factor-mediated reprogramming of PAI-1 gene expression is critical to the normal process of wound repair.

The clinical areas of investigation have focused on developing an understanding of the intrinsic factors (i.e., protease profiles and growth factor profiles) within the wound bed that can either enhance or inhibit normal wound healing. Cultured epidermal allografts can be successfully cryopreserved for long term storage, whereupon they can be retrieved and used to enhance the healing of partial thickness wounds. The ultimate aim of this laboratory is to develop an understanding of the mechanisms governing NHK migration and differentiation in response to wounding and to utilize this knowledge to design more optimal biological wound dressings to enhance the healing of both partial and full thickness burn wounds.

**RECENT PUBLICATIONS**


**Staiano-Coico, L., Carano, K., Allan, V.M., Steiner, M.G., Pagan-Charry, I., Bailey, B.B., Babaar, P., Rigas, B. And Higgins, P.J. PAI-1 gene expression is growth state-regulated in cultured human epidermal keratinocytes during progression to confluence and post-wounding. Exp. Cell Res. 227:123-134, 1996.**

**Mu, X.C., Staiano-Coico, L. and Higgins, P.J. Increased transcription and modified growth state-dependent expression of the plasminogen activator ihibitor type-1 gene characterizes the senescent phenotype in human diploid fibroblasts. J. Cell Physiol. 170:90-98, 1997.**


*Cell Biology & Genetics*

# John L. Stephenson, M.D.

## THEORETICAL AND COMPUTATIONAL RENAL PHYSIOLOGY

The overall goal of our work is to synthesize experimental data at the membrane and molelcular level into predictive mathematical models of the mammalian kidney that are useful in understanding both its normal and diseased function.

Depending on the species, the mammalian kidney consists of a 50,000 to one million similar but not identical units, the nephrons, operating in parallel. Each nephron is a tube approximately 1 cm long and 10-3cm in diameter. The closed end is wrapped around a specialized knot of capillaries to form the glomerulus; the open ends merge to empty into the ureter and thence the bladder. A protein and cell free filtrate of blood expressed by the glomerular capillaries is modified as it flows down the nephron by the selective reabsorption of most of the solutes and water and the selective secretion of other solutes to form the final urine needed to maintain the composition of the interstitial fluid bathing the cells of the body within the narrow limits compatible with life.

Our current research is directed along two parallel paths:

1) Incorporation of the details of transcellular transport into models of individual tubular segments.

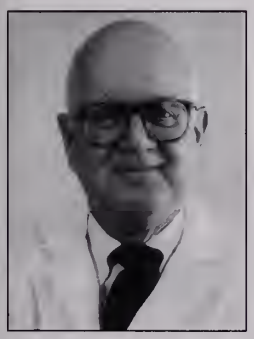
2) Incorporation of the tubular models into architecturally detailed models of single nephrons and of the whole kidney. Simulation of these extended models lends itself naturally to the vector and parallel processing capabilities of supercomputers, and we have ongoing projects at both the Cornell National Supercomputer Facility and at SUNY, Stony Brook.

**RECENT PUBLICATIONS**


**Stephenson, J.L. , H. Wang, and R. P. Tewarson. Effect of vasa recta flow on concentrating ability of models of renal inner medulla. Am. J. Physiol. 1268: F698-F709, 1995.**

**Tang, Y., and Stephenson, J.L., Calcium dynamics and homeostasis in a mathematical model of the principal cell of the corical collecting tubule. J. General Physiol. 107:207-230, 1996.**


*Physiology, Biophysics & Molecular Medicine*



# Peter E. Stokes, M.D.

## NEUROENDOCRINOLOGY

Previous data from our laboratory has shown that Hypothalamic-Pituitary-Adrenal (HPA) axis response to ECT was inversely proportional to the pre-ECT level of HPA activity. Induced high levels of pre-ECT glucorticoid did not alter this, demonstrating this stimulus to be relatively refractory to feedback inhibition. We now want to study in humans the prior data in rats demonstrating age and prior glucocorticoid exposure related hippocampal damage (Landfied), persistent glucocorticoid receptor down regulation (McEwen & Sapolsky) and the cascade hypothesis (Sapolsky) of progressive hippocampal damage and resultant disinhibition of HPA function. Characteristics of HPA response to ECT with and without prior enhanced glucocorticoid feedback will be studied as regards peak response, time to peak, area under response curve and duration of response above baseline in relation to age and pre-ECT level of HPA activity. Our data to date showing duration of post-ECT HPA response to stress is evident in aged animals with disinhibited HPA function secondary to inhibition of ACTH release after ECT in patients with elevated tissue cortisol levels (enhanced negative feedback) and/or secondary to pituitary CRH receptor down-regulation from chronically increased hypothalamic CRH release associated with the stress of depression.

**RECENT PUBLICATIONS**


**Kathol R.G., Poland R.E., Strokes P.E., Wade S. Relationship of 24-hour urinary free cortisol to 4-hour salivary morning and cortisol and cortisone as measured by a time-itegrated oral diffusion sink. Journal of Endocrinological Investigation 18 5: 374-377, 1995.**

**Beasley, C.M., Tollefson, G., Tran, P., Satterlee, W., Sanger, T., Hamilton, S. and the Olanzapine HGAD Study Group. Olanzapine versus placebo and haloperidol: Acute phase results of the north american double-blind olanzapine trial. europsychopharmacology 14 2: 111-123, 1996.**


*Neuroscience*

# Ching-Hwa Sung, Ph.D.

## MOLECULAR GENETICS AND CELL BIOLOGY OF RETINAL DEGENERATION

Retinitis pigmentosa (RP) is a group of inherited disorders characterized by night blindness and progressive photoreceptor death, leading eventually to blindness. The prevalence of RP is approximately 1 in 4,000, and it is one of the leading causes of inherited blindness in the human population. To better understand the molecular basis and pathogenic mechanisms of RP is the first step toward more effective therapies for RP. Previously, we have identified mutations in the gene encoding rhodopsin, a visual pigment of rod photoreceptors, in patients with RP. Subsequently, we studied the biochemical defects of these mutant proteins in tissue culture cells as well as in transgenic mice.

We are currently focused on unraveling the pathogenesis of RP caused by a particular class of mutations which were mapped near the carboxy terminus of rhodopsin. Our previous studies have indicated that the cytoplasmic tail of rhodopsin mediates its vectorial transport from its site of synthesis in the photoreceptor cell body to the outer segment. The impairment of this function of rhodopsin in RP patients somehow leads to cell death. To search for the machinery responsible for targeting and/or transporting rhodopsin *in vivo*, we have identified proteins that interact with the carboxy-terminus of rhodopsin using two-hybrid screening. We are in the progress of determining the molecular identities of the isolated proteins and examining the physiological significance of these interactions *in vivo*. We are also testing the possibility that mutations in the genes of rhodopsin's interacting proteins cause RP or related retinal dystrophies.

In parallel, we have studied the sorting signal of rhodopsin in polarized epithelial cells since previous results suggested that neuronal and epithelial cells may share common pathways in sorting membrane proteins. Our results suggest that the carboxy-terminal tail of rhodopsin contains a novel cytoplasmic apical sorting determinant and we hope to identify the apical sorting receptor responsible for this vectorial transport in the polarized epithelial cells.

**RECENT PUBLICATIONS**


**Chuang, J.-Z., and Sung, C.-H. The carboxy-terminus of rhodopsin functions as an apical sorting signal in MDCK cells. J. Cell Biol. 142: 1245-1256, 1998.**

**Tai, A.W., Chuang, J.-Z., and Sung, C.-H. Localization of Tctex-1, a cytoplasmic dynein light chain, to the Golgi apparatus and evidence for dynein complex heterogeneity. J. Biol. Chem. 273: 19639-19649, 1998.**


*Neuroscience*

*Cell Biology & Genetics*

# Hazel H. Szeto, M.D., Ph.D.

## OPIOID PEPTIDES AND RECEPTORS

We are interested in understanding the functional roles and mechanisms of action of opioid peptides and receptors in neuroendocrine and cardiovascular regulation. We are currently focusing our attention on two actions of opioid peptides that were recently observed in the intact animal: the release of adrenocorticotropin (ACTH) and insulin by dynorphin that does not appear to be mediated by opioid receptors, and the increase of cardiac output by synthetic opioid peptides that act on mu opioid receptors. We are currently trying to identify the receptor and signaling pathways involved in the secretory actions of dynorphin on anterior pituitary cells and pancreatic. In the isolated heart, we have found that mu opioid peptides can exert opposing actions on the force of contraction that appear to be dependent on the initial conditions of the heart, with a decrease in contractility in healthy hearts, and an increase in contractility in failing hearts. We are currently trying to identify the cellular mechanisms behind this paradoxical effect of mu opioid peptides on cardiac contractility. A better understanding of these actions of opioid peptides and receptors are important in the clinical use of the opioid drugs for analgesia.

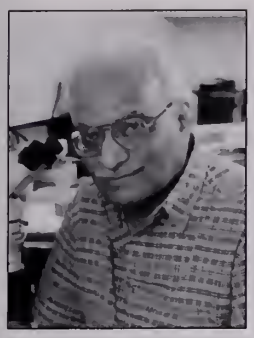
Another focus of our laboratory is the design of new and improved opioid analgesics for use in obstetrics. The goal is to minimize adverse effects on the fetus by considering maternal-fetal pharmacokinetics and receptor selectivity. To this end, we are comparing a series of novel synthetic opioid peptide analogs that have varying physicochemical characteristics and receptor selectivity. The project involves a comprehensive evaluation of the pharmacokinetics and pharmacodynamic effects of these peptides in the maternal-fetal unit using the pregnant sheep model.

**RECENT PUBLICATIONS**


**Taylor, C.C., Wu, D.L., Soong, Y., Yee, J. and Szeto H.H: Dynorphin A-(1-13) stimulates ovine fetal pituitary-adrenal function through a novel nonopioid mechanism. J. Pharmacol. Exp. Ther. 280:416-421, 1997.**

**Taylor CC, Yee JS, Wu DL, Soong Y and Szeto HH: Opioid modulation of the fetal HPA axis: The role of receptor subtypes and route of administration. J. Pharmacol. Exp. Ther. 281:129-135, 1997.**


*Pharmacology*



# Suresh S. Tate, Ph.D.

## MOLECULAR BASIS OF MAMMALIAN AMINO ACID TRANSPORT

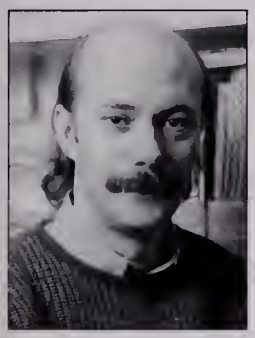
Amino acids (aa's) are essential ingredients of human nutrition. The so-called "essential aa's" must be obtained from diet. Their transport into cells is, thus, a vital process, defects in which can lead to disease. Thus, cystinuria, is an autosomal recessive disease in which excessive amounts of cystine and basic aa's are excreted in urine. The low solubility of cystine results in formation of kidney stones and, eventually, renal failure. Three types of cystinurias have been described. All involve defects in a high-affinity transport system for cystine in kidney and intestinal epithelial cells. The molecular basis of this transport is not fully understood. A kidney protein, NBAT, cloned by us, has been implicated in this transport, and mutations in human NBAT have been found in several cystinurics, making it a promising candidate for a cystinuria gene. However, mutations in NBAT were found only in Type I cystinurics suggesting that defects in other, as yet uncharacterized, genes may be responsible for the Types II and III syndromes. Recently, we showed that kidney and intestinal NBAT is associated with another protein (approximately 50 kDa) and proposed that this heterodimer represents the functional unit of the cystine transporter, an unusual model for a metabolite transporter. We are currently attempting to clone this associated protein and elucidate its role, along with that of NBAT, in epithelial cystine transport. Our projected studies are expected to enhance our understanding of the molecular mechanisms involved in epithelial cystine and basic aa transport, and of the molecular and genetic factors responsible for producing the cystinuric syndrome.

**RECENT PUBLICATIONS**


**Wang, Y. and Tate, S.S. Oligomeric structure of a renal cystine transporter: Implications in cystinuria. FEBS Lett. 368:389-392, 1995.**

**Tate, S.S. Evidence suggesting that the minimal functional unit of a renal cystine transporter is a heterodimer and its implications in cystinuria. Amino Acids 11:209-224, 1996.**


*Biochemistry & Structural Biology*



# Paul Tempst, Ph.D.

## PEPTIDE ANTIBIOTICS AND MICRO-CHEMISTRY

The principal interest of the structural chemistry group is to improve technology, strategies and micro-methods for polypeptide isolation, and for mass spectrometric protein identification and mapping of modified amino acids. Our program draws from conventional biochemistry but also from the fields of chemistry and engineering. The novel tools have found widespread use in the health and life sciences; as a resource for the larger research community and for our own studies on peptide antibiotic expression and function.

*Apidaecin*, an insect peptide isolated by our group is lethal for gram negative bacteria. Killing is the result of interaction with chiral target(s) in the bacterial cell and may be situated at the level of biopolymer synthesis. Identification of these targets may provide the scientific basis for rational design of novel antimicrobial compounds, and is the focus of our research. Structure-function studies have allowed us to dissect the sequence in 'constant' and 'variable' regions, responsible for, respectively, general antibacterial capacity and specificity of the antibacterial spectrum. The underlying biochemical mechanisms are being investigated.

*Defensin* peptides are prominent constituents of human neutrophils and play a role in innate host defense. Transcription begins at the promyelocytic stage and is distinctively regulated during further differentiation. Transcript levels are also greatly affected by modulation of multiple protein kinase activities, even in the absence of maturation. While manifest in leukemic promyelocytic cells, cAMP-dependent induction does not occur in other cell types. Thus, both cell specific factors and common kinases are pivotal for activation. We have mapped a genomic element that directs cell specific gene expression *in-vivo*. In addition, two small (15 bp) fragments thereof interact with PU.1 and with a retinoic acid inducible nuclear phosphoprotein. We are in the process of locating all control element(s), and isolating and characterizing putative novel factors that control promyelocytic expression of *defensin*.

**RECENT PUBLICATIONS**


**Geromanos, S., Philip, J., Freckleton, G., and Tempst, P. Injection adaptable fine ionization source ('JaFIS') for continuous flow nano-electrospray. Rapid Commun. Mass Spectrom. 12:1-6, 1998.**

**Ma, Y., Su, Q., and Tempst, P. Differentiation-stimulated activity binds an ETS-like, essential regulatory element in the human promyelocytic *defensin-1* promoter. J. Biol. Chem. 273:8727-8740, 1998.**


*Biochemistry & Structural Biology*

*Molecular Biology*

# Jon S. Thorson, Ph.D.

## BIOSYNTHETIC CHEMISTRY

Historically, biology has provided unique lead compounds as targets for the synthetic organic chemist interested in drug discovery. In contrast to a conventional synthetic chemistry approach, my laboratory strives to focus not upon the natural product as the objective but upon the natural catalysts (enzymes) that construct therapeutically useful metabolites. Our detailed mechanistic understanding of the enzymes involved in these biosynthetic pathways, through the use of tools ranging from molecular biology to organic chemistry, will provide the basis for their exploitation to engineer novel and highly effective therapeutic agents. Efforts are underway in the following arenas:

*Calicheamicin* is a remarkable example of bacterial (*Micromonospora*) engineering to provide a complex molecule endowed with three essential functional domains: a) a "warhead" destined to "explode" upon suitable activation, thus providing the fragments that damage DNA; b) a "delivery system" which delivers the warhead to its target, DNA; and c) a "triggering device," which initiates the cascade of reactions that leads to the generation of DNA damaging radicals. We are focusing upon the elucidation of the mechanistic details of calicheamicin biosynthesis/resistance and the exploitation of this unprecedented biosynthetic pathway to engineer new and highly effective antitumor/antibacterial agents. Toward this goal we have successfully cloned the gene cluster encoding the calicheamicin biosynthetic/resistance enzymes/proteins and are initiating a combinatorial biosynthesis program toward novel calicheamicin analogs.

*Glycosyltransferases* are the catalysts responsible for constructing the critical glycosylation patterns of cell surfaces (essential for cellular molecular recognition), glycoproteins and antitumor/antibiotic compounds. Our focus is upon understanding and exploiting glycosyltransferase-catalyzed oligosaccharide synthesis and the use of gene-shuffling/screening methods to engineer novel glycosyltransferases capable of new glycosylation reactions. With a variety of simple prokaryotic model glycosyltransferases in hand, we are also considering methods for the display of "useful" carbohydrate antigens on bacterial surfaces to be used as live vaccines.

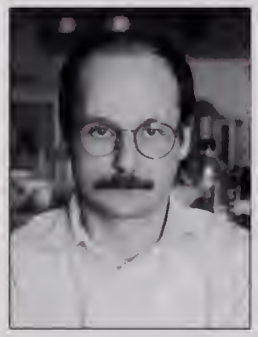
**RECENT PUBLICATIONS**


**Zhao, Y., Biggins, J.B. and Thorson, J.S. A Comparison of Nucleotide Sugar Synthetic Methodology and Its Relevance to a General Prokaryotic Mannosyltransferase Assay. J. Am. Chem. Soc. (In press) 1998.**

**Zhao, Y., Biggins, J.B. and Thorson, J.S. Models for Enzymatic Mannosyl Transfer: Synthesis and In vitro Mannosylation of an Unnatural Acceptor for the Development of a Novel Prokaryotic Mannosyltransferase Assay. J. Am. Chem. Soc. (in press) 1998.**


*Pharmacology*

*Biochemistry & Structural Biology*



# Miklos Toth, M.D., Ph.D.

## MOLECULAR PATHOGENESIS OF CNS DISEASES MODELED IN TRANSGENIC AND KNOCKOUT MICE

The goal of the laboratory is to study the molecular pathogenesis of CNS disorders. The main approach is to alter the expression of candidate disease genes in mice, resulting in conditions analogous to human disorders. The ultimate goal is to identify key disease-causing pathways and mechanisms and to find molecular targets for drug intervention and gene therapy.

One direction is to study the pathomechanism of epilepsy. We identified a novel gene *(jerky)* whose mutation leads to epilepsy in mice. Jerky is an mRNA binding protein which is functionally similar to the fragile X syndrome protein FMRP. Jerky is likely involved in the transport and/or translation of a subset of mRNAs. The goals of the current work are to specify the mRNA targets for jerky and to characterize the jerky-RNA complex which could lead to a better understanding of the patmomechanism of epilepsies.

Another focus is to study the monoaminergic (serotonin, dopamine, and phenylethylamine) system and its involvement in neuropsychiatric disease. Disturbances of these systems occur in depression, anxiety, drug abuse, and stress-related disorders. To identify important disease-causing mechanisms, the monoamine system has been disrupted at specific points in the monoamine system. Mice lacking the monoamine catabolizing enzyme MAOB is highly susceptible to stress and shows a high preference to cocaine in an animal model of drug abuse. Since these "symptoms" are often seen in neuropsychiatric disease, we are presently studying the pathogenic process that underlie the phenotype. Another mouse strain currently studied is deficient for the 5-$HT_{1A}$ receptor and shows anxiety-like behavior. These animals represent a novel genetic model to study the role of the 5-HT system and 5-$HT_{1A}$ receptor in anxiety. The main objective of this work is to determine the neurobiological mechanism that underlies the anxiety-like behavior in receptor deficient mice.

**RECENT PUBLICATIONS**


**Grimsby, J., Toth, M., Chen, K., Kumazawa, T., Klaidman, L., Adams, J. D., Karoum, F., Gal, J., and Shih, J.C. Mice lacking MAOB show marked increases in ß-phenylethylamine, stress responsiveness, and resistance to MPTP toxicity. Nature Genetics. 17, 206-210, 1997.**

**Parks, C., Sibille, E., Robinson, T., Shenk, T., and Toth, M. Increased anxiety of mice lacking the serotonin1A receptor. Proc. Natl. Acad. Sci. USA. (in press), 1998.**


*Neuroscience*

*Pharmacology*

# Rosario Trifiletti, M.D., Ph.D.

NOVEL MECHANISMS IN NO TOXICITY

We have been studying mechanisms of nitric oxide toxicity that contribute to neurological disease. Recently, we have focused upon protein tyrosine nitration, a relatively specific effect of NO-derived peroxynitrite, on a variety of proteins. We have been examining protein tyrosine nitration in a number of animal models of disease and in tissues of patients with a number of neurological diseases.

Also, in collaboration with Dr. John Wagner's laboratory, we have discovered a novel biochemical response to NO/peroxynitrite, the stimulation of endogenous protein biotinylation. Nitric oxide, superoxide and peroxynitrite stimulate formation of a specific biotinylated protein (which we have termed bp160) in a p21ras-dependent fashion. The molecular nature of the biotinylated target proteins and the significance of this finding in NO toxicity is being investigated.

IMMUNOCHEMICAL MECHANISMS IN PEDIATRIC NEUROPSYCHIATRIC DISORDERS

A relationship between the relatively common pediatric neuropsychiatric disorders Gilles de la Tourette syndrome (Tourette syndrome; TS) and obsessive-compulsive disorder (OCD) has long been suspected. Recent data strongly suggests an autoimmune basis for at lease some cases of TS or OCD based on a variety of clinical and laboratory observations suggesting a relationship to Sydenham chorea, an aspect of rheumatic fever long established to have an autoimmune post-streptococcal basis.

We have discovered that almost all patients with TS or OCD specifically bear serum antibodies to a protein found in normal human brain of apparent molecular weight 83-kilodaltons, that we have termed ts83. Partial sequence analysis of ts83 indicates similarity to a tissue-specific calpain, a member of a family of proteases with diverse biological roles. We are currently actively extending these findings in order to attempt to elucidate the molecular pathophysiology of TS and OCD. In this effort, we are actively collaborating with the laboratories of Dr. Margaret Altemus (CUMC Dept of Psychiatry) and Dr. John Zabriskie (Rockefeller University).

**RECENT PUBLICATIONS**


**Nguyen, K., Wagner, J.F. and Trifiletti, R.R. Nitric oxide stimulates endogenous protein biotinylation in neural cells by p21ras-dependent and independent pathways. Submitted, J. Neurosci (1998).**

**Trifiletti. R.R., Delanty, N Bandele, A..N., Lynch, T. and S. Przedborski, Elevated protein nitrotyrosine immunoreactivity in cerebrospinal fluid of patients with amyotrophic lateral sclerosis Submitted, Neurology (1998).**

**Trifiletti R.R., Frucht S., Altemus, M., Bandele, A. and J. Zabriskie. TS83: a candidate autoantigen recognized by the serum of patient with Gilles de la Tourette Syndrome and obsessive compulsive disorder. Submitted, Proc Nat'l Acad Sci USA (1998).**


*Neuroscience*

# Jonathan Victor, M.D., Ph.D.

VISUAL INFORMATION PROCESSING, MATHEMATICAL MODELLING OF NEURAL PROCESSES, NONLINEAR DYNAMICS

How are form, color, and motion extracted from the visual image, and how do these submodalities interact? How are unambiguous percepts represented in neural spike trains, which are intrinsically ambiguous? What are realistic models for how visual information is transformed by neurons of the mammalian visual system? How does disease of the nervous system affect these processes? What are the intrinsic dynamics of networks of neurons in normal brain and in epilepsy? We are addressing these questions at multiple levels: behavior (via psychophysical studies in man), cell populations (via surface and depth evoked potentials), and at the cellular level (via single-unit recording). These experimental studies are accompanied by theoretical investigations. What are appro priate mathematical models for complex biological systems, and how can they be tested empirically? What are the general rules for how the properties of a large, complex system derive from the properties of its constituents and their connections?

**RECENT PUBLICATIONS**


**Mechler, F., Victor, J.D., Purpura, K.P, and Shapley, R. Robust temporal coding of contrast by V1 neurons for transient but not steady-state stimuli. J. Neurosci. 18: 6583-6598, 1998.**

**Victor, J.D., and Purpura, K.P. Metric-space analysis of spike trains: theory, algorithms, and application. Network 8: 127-164, 1997.**


*Neuroscience*

# Bruce T. Volpe, M.D.

## MECHANISMS OF NEURON DEGENERATION, CLINICAL MECHANISMS OF MOTOR RECOVERY

Neurodegenerative diseases of aging are insidious, and unrelenting. There are models and techniques that now permit the exploration of chronic neuronal pathophysiology that unfolds after a primary insult. Experiments in our laboratory have demonstrated in vivo that an imbalance of afferent projections to a target region can cause delayed transneuronal degeneration. Recent in vivo experiments have reversed the unbalanced glutamate influence with NMDA receptor blockers and have significantly protected neurons in the target nucleus. Further in vivo experiments have demonstrated effective strategies to protect neurons from the degenerative process by the application of growth factors. Techniques employ systems neuroanatomy, stereotaxic surgery, quantitative immuno-histochemistry, receptor autoradiography, pharmcological intervention, and functional analysis. Future experiments will describe the time course of the degeneration, test whether specific antagonists are also protective, whether the degeneration involves apoptosis or dysregulation of Ca or both. Another goal of the project is to develop a transgenic animal in which the problems of chronic neurodegeneration can be studied.

Patients with ischemic injury to the cortex and basal ganglia demonstrate superior functional outcome to patients with volumetrically smaller ischemic damage confined to the basal ganglia (Miyai, I., et al., Neurol. 48:95-101, 1996). These descriptive analyses will permit a test of different treatment strategies (Krebs HI,et al.,. IEEE, Trans.Rehab. Eng., 1, 75-87, 1998). Besides pharmacological and physical medicine therapies, experiments will also test new robot aided neuro-rehabilitation techniques (Aisen, M.L.,et al., Arch. Neurol. 54:443-446 1997).

**RECENT PUBLICATIONS**


**DeGiorgio L.A., Dibinis, C., Milner, T.A., Sajl, M., Volpe, B.T. Histological and temporal characteristics of nigral transneuronal degeneration after striatal injury. Brain Research 795: 1-9, 1998.**

**Volpe, B.T., Wildmann, J., Altar, C.A. BDNF prevents the loss of nigral neurons induced by excitotoxic striatal lesions. Neuroscience 83: 741-748, 1998.**


*Neuroscience*

# John A. Wagner, Ph.D.

## REGULATION OF NEURAL DEVELOPMENT, DIFFERENTIATION, FUNCTION, AND SURVIVAL BY PEPTIDE GROWTH FACTORS, RETINOIC ACID, NITRIC OXIDE, AND OTHER SIGNALING MOLECULES

Research Interests: Neural development and differentiation, peptide growth factors, signal transduction, rho family of G proteins in neurite outgrowth and neural migration, gene expression, protein kinases, Nitric Oxide, stroke and neurodegenerative disease, and growth factors in the retina.

Description of Research:

1. The small GTP-binding protein, rac, is an important mediator of both process outgrowth and neural migration. We are studying the mechanism of this effect and the role of other members of this family including rho and cdc42 in neural differentiation.

2. An essential component of NGF (Nerve Growth Factor) action is the regulation of gene expression. We have identified NGF-responsive elements in two genes, and we are isolating the transcription factors that are targets of NGF.

3. We recently showed that HES-1, a bHLH transcription repressor, is a key nuclear target of NGF. We are interested in the roles of HES and other bHLH proteins, like MASH, in the repression or promotion of neural differentiation.

4. We are exploring the way peptide growth factors can support the survival of neurons during neurodegenerative disorders. We are particularly interested in the toxic effects of Nitric Oxide during ischemia and the ways these effects can be minimized by growth factors and other signaling systems. Currently, we are focusing on protein biotinylation, a novel NO-dependent post-translational modification that we recently discovered.

5. The FGFs are emerging as important regulators of neural development and differentiation. We discovered that these growth factors can stimulate neurite outgrowth both in vivo and in vitro. We are studying their biochemical mechanism of action and their role during development and during response to neural injury.

6. Growth factors are also important in development and repair in the retina. We are studying growth factors in the retina and we are developing new models of retinal disease.

**RECENT PUBLICATIONS**


**Strom, A., Castella, P., Wagner, J. A., and Caudy, M. Mediation of NGF signalling by post-translational inhibition of HES-1 a basic helix-loop-helix repressor of neuronal differentiation. Genes and Development 11:3168-3181, 1997.**

**Altun-Gultekin. Z.F., Chandriani, S., Bougeret, C., Ischizaki, T., Narumiya, S., Henegouwen, P.V.B., Hanafusa, H., Wagner, J.A. and Birge, R.B. Activation of rho-dependent cell spreading and focal adhesion biogenesis by the v-Crk adaptor Protein. Mol Cell Biol 18:3044-3058, 1998 .**


*Neuroscience*

*Cell Biology & Genetics*

# Yi Wang, Ph.D.

## MAGNETIC RESONANCE (MR) IMAGING

Our prime interests are the science and engineering of magnetic resonance (MR) imaging, and application in clinical practice. Currently we are developing techniques for imaging blood flow in large vessels (angiography) and in microvasculature (perfusion). These techniques are targeted for applications in cardiovascular diseases and neuro-functional mapping.

Cardiac MRI. Cardiovascular diseases is the No. 1 killer in the United States. Non-invasive diagnosis of cardiovascular diseases using MR would significantly advance patient care. For example, screening lesions in coronary arteries in their early stage prior to heart attack would provide a tremendous saving of lives. The challenge to imaging coronary arteries that supply blood to cardiac muscle is motion - cardiac contraction and respiration. This motion is difficult to predict by a model. We are developing techniques based on "imaging in the motion frame." The motion of the heart is sampled with navigator signals, which are processed in real-time and fed back to modify data acquisition accordingly, to eliminate motion artifacts. Substantial computer engineering and image processing are being integrated in this intelligent model-free navigator method.

Functional MRI. Human organ functions depend on and also affect blood supply. Accordingly, tissue perfusion provides assessment of organ function. Neuro-activation of the brain affects blood oxygenation level and perfusion rate. Neuro-function areas in the cortex can be mapped out by dynamic perfusion imaging synchronized to activation. MR brain mapping is one of the most exciting development in neuroscience, but the technology is still at its early stage. We are examining data acquisition strategies to improve signal-to-noise ratio and biophysics models to better understand the relation between activation and MR signal response.

MR Angiography. Our research work applies directly to clinical practice. We have developed non-invasive fluoroscopic MRA - MR digital subtraction angiography (MRDSA), and applied MRDSA to image vascular diseases in the lower extremity. To overcome the problem of the large longitudinal extend in the lower extremity (~ 100 cm, from aortic bifurcation to the feet), we developed a bolus chase MRDSA technique. Angiographic data acquisition follows the peak of the contrast passage (contrast bolus) from the proximal (aortic bifurcation) to distal location (feet), shortening scan time and minimizing contrast dose. Preliminary data confirmed that bolus chase MRDSA is a fast, accurate, and dose-minimized method, and bolus chase MRDSA is now a routine clinical tool at Cornell Medical Center, an non-invasive and economic alternative to x-ray Angiography.

**RECENT PUBLICATIONS**


**Wang, Y., Lee, H.M., Avakian, R., Winchester, P.A., Khilnani, N.M., Trost, D. Timing algorithm for bolus chase MR digital subtraction angiography. Magnetic Resonance in Medicine 39, 691-696, 1998.**

**Lee, H.M., Wang, Y. Dynamic k-space filling for bolus chase 3D MR digital subtraction angiography. Magnetic Resonance in Medicine 40:99-104, 1998.**


*Physiology, Biophysics & Molecular Medicine*

# Alan M. Weinstein, M.D.

## THEORY OF SOLUTE AND WATER TRANSPORT ACROSS EPITHELIA

The primary objective of this laboratory is the development of a mathematical models of the renal epithelia. A mathematical model of the mammalian collecting duct will be developed, comprised of cellular models of cortical, outer medullary and inner medullary segments. The model will represent Na, K, and acid/base transport under normal and pathological conditions, and will predict their renal excretion, given distal delivery. The initial focus will be parameter assignment for normal collecting duct function and during hormonal stimulation. Particular attention will be paid to cell volume regulation, especially in inner medullary collecting duct, which can vary its Na transport rate from brisk reabsorption to secretion, and which faces a wide range in luminal fluid tonicity. The second focus will be simulation of collecting duct dysfunction. In experimental models (ureteral obstruction, amiloride or lithium administration), specific segmental transport defects have been identified. The model will assess the adequacy of known defects to rationalize observed solute excretion patterns. Finally, the model will simulate clinical tests of distal nephron function (e.g. transtubular K gradient; use of diuretics and impermeant anions to depress urinary pH) in order to assess their applicability to infer specific transport defects.

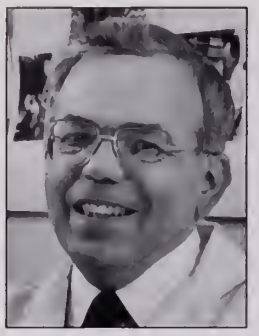
A second aspect of this project is investigation in the theory of cell volume regulation during fluctuations of net transport. In simulations of principal cells and proximal tubule cells, we examine the feasibility of several cellular signals in the control of cell volume. Such signals include pH-dependent K-channels, ATP-dependent K-channels, volume dependent cation and anion channels, and pH-dependent Na/H exchange. The question posed is whether such mechanisms are adequate for the variety of volume challenges encountered by the cell. A theoretical aspect of this work is the development of tools for comparing the efficacy of homeostatic mechanisms in epithelial model systems.

**RECENT PUBLICATIONS**


**Weinstein, A.M. Coupling of entry to exit by peritubular K-permeability in a mathematical model of the rat proximal tubule. Am. J. Physiol. 271: F158-F168, 1996.**

**Weinstein, A.M. Dynamics of cellular homeostasis: recovery time for a perturbation from equilibrium. Bull. Math. Biol. 59:451-481, 1997.**


*Physiology, Biophysics & Molecular Medicine*



# Marc E. Weksler, M.D.

## IMMUNE SENESCENCE

Dr. Weksler's research focuses on the mechanisms underlying the aging process, in general, and the age-associated changes in the immune system in particular. The laboratory studies the effect of age on the immune system of humans and experimental animals. Specifically, we are interested in the molecular and cellular basis for the age-associated dysregulation of the immune system and the contributions of these changes to the increased risk of the elderly to infection and neoplastic disease.

Thymic involution appears to be the pacesetter of immune senescence and directly affects the generation and function of T lymphocytes. Indirectly, impaired T cell function compromises the generation of B cells and their production of antibodies. The impaired production of IL-16 by T cells from old mice explains, at least in part, the decreased expression of RAG genes and the consequent impaired rearrangement of the immunoglobulin gene segments in bone marrow B cell precursors which leads to apoptosis of Pre-B cells in the bone marrow. Recently, we have detected the appearance of monoclonal B and T cell in both elderly humans and old mice. The relationship of these "benign" clonal expansions to late-life leukemia and lymphoma is under study.

**RECENT PUBLICATIONS**


**LeMaoult, J., Delassus, S., Dyall, R., Nikolic-Zugic, J., Kourilsky, P. and Weksler, M.E. Clonal Expansions of B Lymphocytes in Old Mice, J. Immunol. 159:3866-3874, 1997.**

**Szabo, P., Zhao, K., Kirman, I., Dyall, R. Cruickshank, and Weksler, M.E. Maturation of B cell Precursors is Impaired in Thymic-deprived Nude and Old Mice. J. Immunol. in press, 1998.**


*Immunology*

# Martin Wiedmann, Ph.D.

## PROTEIN SYNTHESIS AND PROTEIN TRAFFICKING

Our principal interest is to study protein synthesis and protein trafficking within the cell. The current goal of our research is to dissect the molecular environment of polypeptide chains during their synthesis on the ribosome because at this critical point the cell must ensure that only the appropriate, of many potential, fates of a nascent chain is realized.

Although the principal function of the ribosome is peptide bond synthesis, many cotranslational processes such as protein targeting and folding can occur on the polypeptide associated complex (NAC), which acts cotranslationally at the interface of ribosome and the cytosol. NAC, which is not a core ribosomal protein, is an abundant heterodimeric protein which is present in all tested eukaryotic cells. NAC is in contact with polypeptides almost as soon as they are synthesized. We have demonstrated that the tunnel, through which the nascent chain was thought to move before emerging into the cytosol, consists of the ribosome and NAC, whereby NAC forms a dissociable wall of the "tunnel".

The importance of NAC is further revealed in experiments in which we studied its function during targeting of ribosomes to the endoplasmic reticulum (ER) membrane. It has been known for a long time that signal peptides in conjunction with the signal recognition particle (SRP) direct the cotranslational in vitro targeting of nascent polypeptides to the ER. We have now shown that isolated ribosome-nascent chain complexes are efficiently targeted to the ER independent of the presence of a signal peptide. This targeting is blocked by NAC. To achieve specificity for signal sequence exposure of a putative ribosomal membrane attachment site which binds to receptors present in the ER membrane.

**RECENT PUBLICATIONS**


**Wang, S., Sakai, H. And Wiedmann, M. NAC covers ribosome-associated nascent chains thereby forming a protective environment for nascent chains just emerging from the peptidyl transferase center. J. Cell Biol. 130:519-528, 1995.**

**Lauring, B., Kriebich, G. and Wiedmann, M. The intrinsic ability of ribosomes to bind to ER membranes is regulated by SRP and NAC. Proc. Natl. Acad. Sci., USA 92:9435-9439, 1995.**


*Cell Biology & Genetics*

# Paul A. Wilson, Ph.D.

## REGULATION OF CELL FATE AND BEHAVIOR IN EARLY XENOPUS DEVELOPMENT

In the course of embryonic development, as the rudiments of an animal emerge from the fertilized egg, cells divide, learn their fates, and differentiate into dozens of specialized cell types in precise patterns. At the same time, the cells of the embryo crawl, change shape and rearrange to build organs and tissues. While progress has been made in recent years in identifying the molecular signals that specify cell fate, the control of cell behavior has been much less studied, and the relationship between the two essential tasks of the early embryo is a great unanswered question in developmental biology. In my lab we study these processes — determination, pattern formation, and morphogenesis — in the frog Xenopus laevis, which allows an unmatched combination of molecular genetic, biochemical, and embryological techniques to be brought to bear on the study of embryogenesis. Our work focuses on the events of gastrulation, a critical period in early development during which dramatic tissue movements and a cascade of inductive signals act together to establish the basic vertebrate body plan. These movements are driven in large part by a morphogenetic process called convergent extension, in which cells rearrange to cause many-fold elongation of the dorsal side of the embryo. Although organized cell rearrangement is important in the development of all vertebrates, it remains poorly understood at the cell biological and molecular level. We are working to understand how this complex behavior is initiated and directed, and how these morphogenetic events are integrated with other aspects of pattern formation in the early Xenopus embryo. In particular, we are examining the role of the Wnt signal transduction pathway in gastrulation movements: recent work has suggested that components of this signaling system may be involved in the control of convergent extension. Since the Wnt pathway is also known to regulate cell fate in early development, analyzing its various roles will allow us to explore the mysterious relationship between cell fate determination and the control of cell behavior.

**RECENT PUBLICATIONS**


**Wilson, P.A. & Hemmati-Brivanlou, A. Induction of epidermis and inhibition of neural fate by BMP4. Nature 376: 331-333, 1995**

**Wilson, P.A. & Hemmati-Brivanlou, A. Neural induction and its aftermath. Neuron 18: 699-710, 1997.**


*Cell Biology & Genetics*

# Erich Windhager, M.D.

Dr. Windhager's studies are aimed at elucidating the mechanisms of ion and water transport by renal epithelial cells, in particular the negative feedback regulation of sodium transport in cortical collecting tubules. Combining techniques of measuring transepithelial sodium fluxes, intracellular ion concentrations by fluorescence methods, and patch clamping of ion channels, it was concluded that cytosolic calcium ions and membrane voltage can account for the observed feedback control. In other studies, a new water channel (AQP3) from the renal medulla that is independent of ADH has been expressed in Xenopus oocytes and has been fully cloned.

**RECENT PUBLICATIONS**


**Frindt, G., Palmer, L.G. and Windhager, E.E. Feedback regulation of Na channels in rat CCT IV. Mediation by activation of PKC. Am. J. Physiol. 270:F371-F376,1996.**

**Echevarria, M., Windhager, E.A. and Frindt, G. Selectivity of the renal collecting duct water channel Aquaporin-3. J. Biol. Chem. 271:25079-25082, 1996.**


*Physiology, Biophysics & Molecular Medicine*

# Hao Wu, M.D., Ph.D.

## STRUCTURAL STUDIES OF RECEPTOR SIGNAL TRANSDUCTION

Our laboratory is interested in elucidating the structural mechanisms of receptor signal transduction. Our goal is to determine high resolution three-dimensional structures of key signaling molecules and their complexes using X-ray crystallography and further analyze the structure-function relationships in combination with other biochemical and biophysical methods.

The major part of our research is focused on the regulation of cell survival and cell death by the tumor necrosis factor (TNF) family receptors which include TNFR1, TNFR2, Fas, CD40 and many others. The structural similarities of TNF family receptors are generally limited to their ectodomains while the intracellular domains are fairly diverse, leading to distinct yet overlapping intracellular signaling cascades in response to receptor aggregation by the extracellular ligands. Currently, we are particularly interested in the protein-protein interactions during the early events of this intracellular signaling that eventually leads to apoptosis or cell proliferation and inflammation.

The second part of our research is an extension of our previous work on the human T-cell antigen coreceptor CD4 which also serves as the receptor for the human immunodeficiency virus. CD4 participates in the antigen recognition process by interacting with the class II major histocompatibility complex (MHC) molecules on the surface of antigen presenting cells. This interaction is a key process in normal immune response, malfunction of which has been related to autoimmune diseases. Our structural study on the complex of CD4 with MHC should provide an integral understanding of this interaction in enhancing T-cell recognition.

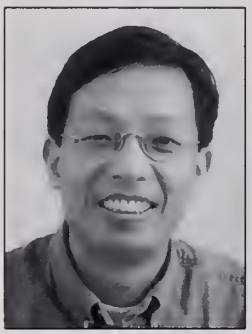
In the course of applying crystallography to enhance our understanding of biological processes, we are actively involved in speeding up the pace of structure solution through computational and experimental renovations. Such advancement would be essential to meet the demand of the ever accelerating pace of discovery of genes and disease genes.

**RECENT PUBLICATIONS**


**Wu, H., Myszka, D.G., Tendian, S.W., Brouillette, C.G., Sweet, R.W., Chaiken, I.M. and Hendrickson, W.A. Kinetic and structural analysis of mutant CD4 receptors that are defective in HIV gp120 binding. Proc. Natl. Acad. Sci. USA 93: 15030-15035, 1996.**

**Wu, H., Kwong, P.D. and Hendrickson, W.A. Dimeric association and segmental variability in the crystal structure of human CD4. Nature 387: 527-530, 1997.**


*Biochemistry & Structural Biology*



# C. Wilson Xu, Ph.D.

## CHEMICAL BIOLOGY

Genetic analysis is a powerful tool for understanding the regulatory networks that govern biological processes. However, the isolation of specific missense alleles is currently impractical for metazoans such as mammals. To develop alternative approaches, we focus on the selection and use of combinatorial biological and chemical ligands that alter the function of proteins *in vivo*. These ligands are analogous to loss- or gain-of-function mutations of the proteins to which they bind. Conditional expression or cell permeablization of these ligands, which is analogous to "non-permissive" conditions, should greatly facilitate the dissection and regulation of signal transduction pathways in mammals.

As proof of this concept, we have developed a yeast two-bait two-hybrid system to identify peptide aptamers that discriminate between active and inactive allelic forms of H-Ras. Some of these apatmers can disrupt the interaction of Ras with its effector c-Raf1, and inhibit the activation of c-Raf1 in mammalian cells. In addition, we have shown that Boolean logic can be used for the dissection of tertiary protein interaction relationships. The logical analysis should also complement classical genetic and biochemical studies for assigning gene function, and play a role in constructing protein linkage maps. We are currently using these new tools to dissect other less-defined signal networks.

Another focus of our laboratory is to understand genetic pathways of catalytic functions. Using directed evolutional approaches, we attempt to synthesize miniaturized enzymes, which we term "pepzymes". Structural and functional studies of these novel enzymes should shed light on the evolution of the catalytic functions.

**RECENT PUBLICATIONS**


**Xu, C.W., Hines, J.C., Engel, M.L., Russell, D.G., and Ray, D.S. Nucleus-encoded histone H1-like proteins are associated with kinetoplast DNA in the trypanosomatid Crithidia fasciculata. Mol. Cell. Biol. 16:564-576, 1996.**

**Xu, C.W., Mendelsohn, A.R., and Brent, R. Cells that register logical relationships among proteins. Proc. Natl. Acad. Sci. 94:12473-12478, 1997.**


*Pharmacology*

# David Zakim, M.D.

## ENZYMOLOGY OF GLUCURONOSYLTRANSFERASE

The focus of this program is the interaction between lipids arranged in bilayers (the solvent) and molecules that dissolve in bilayers (the solutes). The solutes of interest are enzymes that are integral components of bilayers and small organic molecules (not larger than the polymethylene chain region) with limited solubility in water. The biological significance of solvent-solute interactions within the two dimensional solution represented by bilayers is (i) that lipid (solvent) – protein (solute) interactions can regulate the functions of integral membrane enzymes and (ii) that the solubility of small molecules in membranes determines the pathway, tissue specificity, and rate of entry of molecules into cells.

**Lipid-protein interactions.** Microsomal UDP– glucuronosyltransferase is the integral membrane enzyme being studied in this lab. It can be demonstrated for this and all other relevant enzymes studied, that the bulk phase properties (e.g. "fluidity") of lipid bilayers determine function. There is little, if any, direct evidence to support the idea that this widely held view applies to enzymes in biological membranes. Indeed, studies of reconstituted GT show that its functional state depends on microscopic interactions between lipids and proteins. We are trying to delineate the chemical and physical basis for these interactions. The methodology includes classical enzymological techniques using pure, reconstituted enzyme and enzyme in microsomes, and an array of physical techniques for correlating structure and function.

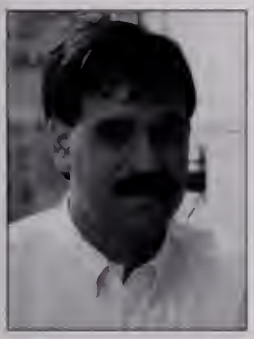
**Solubility of small molecules in lipid bilayers.** An array of small organic molecules with limited solubilities in water are being used to determine the detailed factors regulating solubility in the lipid bilayer portion of membranes. Solubilities are correlated with the effect of the solute on the properties of the solvent and vice-versa. The major techniques for these studies are flourescence and infrared spectroscopy.

**RECENT PUBLICATIONS**


**Kavecansky, J., Dannenberg, A.J. and Zakim, D. Effects of high pressure on the catalytic and regulatory properties of UDP-glucuronosyltransferase in intact microsomes. Biochem 31:162-168, 1992.**

**Noy, N., Leonard, M. and Zakim, D. The kinetics of interactions between bilirubin and lipid bilayers and serum albumin. Biophys Chem 42:177-188, 1992.**


*Cell Biology & Genetics*



# Andrew D. Zelenetz, M.D., Ph.D.

## LABORATORY OF MOLECULAR HEMATO-ONCOLOGY

The laboratory is involved with translational research at the interface between basic laboratory investigation and clinical medicine. To this end, investigation in the laboratory includes three areas of investigation: understanding the basic molecular biology of human lymphomas and leukemias; developing novel therapeutic approaches based on a molecular understanding of disease; and application of molecular techniques to the monitoring of clinical outcomes in patients.

With respect to the first goal we have been investigating molecular pathogenesis of human follicular lymphoma. This disease is characterized by the over expression of the anti-apoptotic gene BCL2 as a result of a chromosomal translocation t(14;18). However, evidence from this laboratory and others suggests that overexpression of BCL2 alone is insufficient to result in malignant transformation. We have previously demonstrated that one of the critical steps in the pathogenesis of the follicular lymphoma is antigenic driven clonal selection. We are attempting to define additional events which are critical in the pathogenesis of this tumor. We have also been studying the molecular pathogenesis of acute promyelocytic leukemia (APL). In this leukemia a novel transcription factor is created as the result of the t(15;17) chromosomal translocation by the fusion of the PML and RARalpha. However, like follicular lymphoma the translocation alone is not sufficient for the generation of the malignant phenotype. In our investigation of the t(15;17) chromosomal translocation, we identified a 25 kilobase repeat unit downstream of the PML gene. The repeat encodes one of a family of golgin-like proteins. Two members of the golgin-like family are expressed in APL. The expression of these genes are downregulated by all- trans-retinoic acid and arsenic trioxide which cause clinical remissions in patients. We are investigating the role of the golgin-like protein in the pathogenesis of APL.

The laboratory is also interested in developing novel therapeutic approaches to the treatment of malignant lymphoma. We have focused on immunotherapy approaches to lymphoma. CD20 is a 35 kilodalton membrane protein which is expressed on all B-cells. The protein is neither modulated upon binding a monoclonal antibody nor is it shed into the serum. These properties make it a very attractive target for immunotherapy. We are developing novel therapeutic approaches aimed at this molecule including vaccination and radioimmunotherapy.

In addition, the laboratory is interested in developing molecular assays which will allow us to test minimal residual disease (MRD) in patients with malignant lymphoma.

**RECENT PUBLICATIONS**


**Zelenetz, A.D., Chen, T.T., and Levy, R. Clonal expansion in follicular lymphoma occurs subsequent to antigenic selection. J. Exp. Med. 176:1137-1148, 1992.**

**Goy, A., Passalaris, T., Xiao, Y.-H., Miller Jr,. W.H., Siegel, D.S., and Zelenetz, A.D. The PML gene is linked to a megabase-scale insertion/deletion restriction fragment length polymorphism. Genomics 26:327-333, 1995.**


*Molecular Biology*

# Ronald D. Adelman, M.D.

## GERIATRICS AND GERONTOLOGY

Ronald Adelman, M.D. is the Medical Director of the Irving Wright Center of Aging and Co-Chief of the Division of Geriatrics Medicine and Gerontology at The New York-Presbyterian Hospital. Dr. Adelman comes to Cornell from Winthrop-University Hospital, where he established the Division of Geriatrics and developed and directed The Fellowship Program in Geriatrics. In conjunction with his tenure at Winthrop, Dr. Adelman was also the Executive Medical Director of the United Presbyterian Residence, a 700 resident nursing home. As Medical Director, Dr. Adelman formulated a curriculum to enhance the training in geriatrics and gerontology for medical students, medical residents, and geriatric fellows.

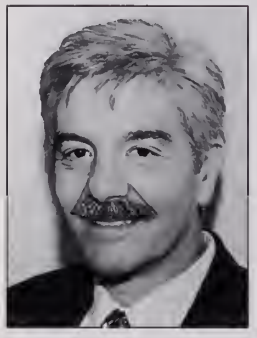
Dr. Adelman's primary area of research concerns the medical encounter and the dynamics of the communication process between older patients and their physicians. His approach to study in this area is multidisciplinary, involving social scientists and physicians from other sub-specialties. With the goal of improving health outcomes among older adults who seek longitudinal health care services from out-patient primary care practices, Dr. Aldeman's research suggests that successful relationships between older patients and their physicians will allow for discussion of sensitive topics, alleviate patient stress, improve patient knowledge, and enable older patients to be more astute users of health care services. Dr. Aldeman is also studying hospice nurse interactions with terminally ill patients.

**RECENT PUBLICATIONS**

**Adelman, R., Siddiqui, H., and Foldi, N. Approaches to Diagnosis and Treatment of Elder Abuse and Neglect. Handbook of Clinical Geropsychology, Plenum Publishing Company, New York, 1998.**

**Adelman, R. and Kaufman, S. Conceptual Framework for the Study of Older Patient-Physician Interactioin. Conference Proceedings of the National Institutes of Aging. Research Issues Related to Physician-Elderly Patient Interactions 1998.**

*Clinical Epidemiology*



# George S. Alexopoulos, M.D.

## GERIATRICS AND GERONTOLOGY

George Alexopoulos, M.D. is a Professor of Psychiatry at Weill Medical College of Cornell University. His research has been guided by the hypothesis that geriatric depression is a heterogeneous entity that includes patients in whom aging-related processes and neurological brain diseases modify the course of illness and the effects of treatment. Through a series of cross-sectional studies, Dr. Alexopoulos and his colleagues observed that late onset depressives have higher prevalence of dementia than early-onset depressives of similar age. When not demented, late-onset depressives appear to have stigmata of neurological dementing disorders, including cognitive dysfunction, structural brain abnormalities and increased platelet monoamine oxidase activity. His lab has previously characterized the heterogeneity of geriatric depression, tested its response to acute pharmacological treatment, and described its course under naturalistic conditions. Recent studies have sought to identify the timetable and predictors of recovery in elderly patients with major depression and investigate the relationship of disability to the clinical parameters that are part of a comprehensive psychiatric examination of depressed elderly patients. Dr. Alexopoulos and his co-workers identified and defined distinct stages of geriatric depression, e.g., period from onset to recovery, period preceding recovery, or period preceding relapse, etc. Using survival analysis, growth curve analysis and regression methods, they now are studying clinical, neuroradiological (volumes of brain structures) and pharmacological determinants of depressive symptomatology and other outcomes (cognitive impairments, disability) in patients with distinct course of illness, e.g., patients who achieve early relapse after recovery vs. patients with long time to relapse. Using this approach, Dr. Alexopoulos and his co-workers identified two biologically meaningful dimensions of geriatric depression. Dysfunction of the prefrontal-basal ganglia system was found to be associated with slow response to antidepressant treatment and early relapse, while memory dysfunction was found to not 'influence' but rather to predict the development of dementia. These studies may guide geriatric antidepressant treatment practice and provide the background for sharply focused investigations of the mechanisms of specific geriatric depressive syndromes.

**RECENT PUBLICATIONS**

**Alexopoulos, G.S. (with Meyers, B.S., Young, R.C., Kakuma, T., Sibersweig ,D. and Charlson, M.). Clinically defined vascular depression. Am J Psychiatry: 154: 562-565, 1997.**

**Alexopoulos, G.S. (with Meyers B.S., Young, R.C., Campbell, S., Silbersweig, D., Charlson, M.). The "vascular depression" hypothesis. Arch. Gen. Psychiatry 154: 915-922, 1997.**

*Clinical Epidemiology*

# John P. Allegrante, Ph. D.

## BEHAVIORAL SCIENCE, HEALTH PROMOTION AND DISEASE PREVENTION

John Allegrante, Ph.D. is a behavioral scientist and professor of health education on the faculties of Teachers College and the School of Public Health at Columbia University. He has been responsible for leading a broadly conceived program of graduate training and research in health promotion and education there since 1979. In addition to his training and extensive experience in health education, during 1987-88 he was a Pew Health Policy Fellow at the RAND/UCLA Center for Health Policy Study in Santa Monica, California, where he pursued advanced study in health policy and health services research. Dr. Allegrante's research focuses on the design and evaluation of behavioral and educational intervention programs for patient and community populations. Since 1988, he has pursued a consortium-based program of research and development with colleagues at the Hospital for Special Surgery and New York Hospital-Cornell Medical Center that has focused on the prevention of disability due to arthritis and musculoskeletal diseases. He and his team of co-investigators were the first to demonstrate that an intervention program combining supervised fitness walking and socially supportive patient education could produce clinically meaningful improvements in functioning without exacerbating symptoms of pain or increasing use of medication in patients with osteoarthritis of the knee. The Health Care Financing Administration recently cited this research in issuing its guidelines and recommendations for exercise in older persons. Dr. Allegrante is currently leading a team of investigators that is conducting a 5-year, randomized controlled trial designed to evaluate the impact and cost-benefits of a novel intervention program to reduce risk factors for poor functional outcomes and institutionalization following hip fracture.

**RECENT PUBLICATIONS**


**Allegrante, J.P. The role of adjunctive therapy in the management of chronic nonmalignant pain. American Journal of Medicine, 101 (suppl. 1A):33S-39S, 1996.**

**Allegrante, J.P. (with Ruchlin, H.S., Einstein, J., O'Doherty, J., Robbins, L., Peterson, M.G.E., MacKenzie, C.R., Cornell, C.N.). A method for documenting the economic efficacy of multiple-component interventions designed to enhance functional and social status. Arthritis Care and Research, 10: 151-158, 1997.**


*Clinical Epidemiology*

# Josephine A.V. Allen, Ph.D.

## HEALTH POLICY, ECONOMICS AND HEALTH SERVICES RESEARCH

Josephine Allen, Ph.D., ACSW, is an Associate Professor in the Department of Policy Analysis and Management at Cornell University. She is Director of the Baccalaureate Social Work Program, and teaches in both the baccalaureate and graduate programs in the Department of Human Service Studies. She co-chaired the Program on Gender and Social Change at Cornell University. She is a member of the board of the Bronfenbrenner Life Course Center. Her research focuses on comparative social policy, the strengths and coping strategies of mother-only families, empowerment and family support, and the roles and status of professional women in Africa and the African Diaspora. With Ford Foundation funding, she has studied empowerment and family support, tackling the issue of empowerment, gender and social change in Africa and the African-Diaspora. This project had a special focus on recruiting and mentoring graduate students from underrepresented ethnic and racial minority groups.

**RECENT PUBLICATIONS**


**Allen, J.A. Caribbean Americans. Encyclopedia of Social Work. 19th Edition. National Associate of Social Workers. Washington, D.C., 1994.**

**Allen, J.A. Women and Development Strategies for Impacting on Public Policy. Women and trhe Management of Change. Edited by Elsa Leo-Rhyne University of the West Indies. Mona, Jamaica, 1994.**


*Clinical Epidemiology*

# Mitchell J. Blutt, M.D., MBA

Management and Finance

Mitchell J. Blutt M.D., M.B.A., is an adjunct Assistant Professor of Medicine at Cornell. He sees patients at Cornell Internal Medicine Associates, the general medicine faculty practice at Cornell. A former Robert Wood Johnson Foundation Clinical Scholar, Dr. Blutt is a graduate of the University of Pennsylvania and holds an MBA from the Wharton School of Business. While at the Wharton School, Dr. Blutt was awarded the Henry J. Kaiser Family Foundation Prize for his outstanding performance, his exceptional success, and his contributions to the field of health care. Dr. Blutt is also a fellow of the New York Academy of Medicine, a member of the Columbia University Council for the Study of Addiction and Substance Abuse (CASA), and a member of the Agenda for Excellence Council for the University of Pennsylvania. Dr. Blutt's major interest is in the area of entrepreneurship and business development in the health care industry. As our faculty expert on the business aspects of health care, Dr. Blutt has a wide array of experience to draw on. His is the executive partner of Chase Capital Partners (CCP), a company which locates, structures, negotiates and finances acquisitions and venture capital transactions in the health care industry.

*Clinical Epidemiology*

# Gilbert J. Botvin, Ph. D.

BEHAVIORAL SCIENCE, HEALTH PROMOTION AND DISEASE PREVENTION

Gilbert J. Botvin, Ph.D., a Professor of Psychology, holds a joint appointment in the Departments of Public Health and Psychiatry. Dr. Botvin has a national reputation as a behavioral scientist involved in the areas of health promotion and disease prevention, and is widely recognized as an expert in the field of tobacco, alcohol, and drug abuse prevention. Dr. Botvin has been a principal investigator on 20 federally-funded school-based prevention projects involving over 300 schools and 40,000 students. He is currently the Principal Investigator on several NIDA-funded grants including a 10-year drug abuse prevention follow-up study, a drug abuse and violence prevention trial with inner-city youth, and a center grant with collaborators at Columbia University focusing on drug abuse prevention with multi-ethnic youth. Dr. Botvin is also Director of CUMC's Institute for Prevention Research. The mission of the Institute is to promote physical and mental health, and reduce premature death and disability by focusing on the behavioral risk-factors associated with many of the major public health problems. The principal activities of the Institute involve research, professional training, and public education. Dr. Botvin has served as a member or consultant to numerous federal and state agencies, expert advisory panels, and NIH grant review committees. Included among these are the National Cancer Institute, the National Institute of Drug Abuse, the National Heart, Lung, and Blood Institute, the Center for Substance Abuse Prevention, the Center for Disease Control and Prevention, the US Department of Education, and the White House Office on National Drug Control Policy.

**RECENT PUBLICATIONS**

**Botvin, G.J. and Schnike, S. The Etiology and Prevention of Drug Abuse Among Minority Youth. Binghamton, NY: Haworth Press. 1997.**

**Botvin ,G.J., Epstein, J.A., Baker, E., Diaz, T., Ifill-Williams, M., Miller, N. & Cardwell, J., School-based drug abuse prevention with inner-city minority youth. Journal of Child and Adolescent Substance Abuse 6:5-20, 1997.**

*Clinical Epidemiology*

# Robert M. Braude, M.L.S., Ph.D.

## INFORMATION SYSTEMS AND EDUCATION

Robert Braude, Ph.D. has been an academic health sciences library director for over twenty years with an outstanding record in the management of information resources and planning for the implementation of information technology. In addition to his position as The Frances and John Loeb Librarian, he is also the Assistant Dean for Information Resources for the Cornell University Medical College with responsibility for the Cornell Medical Library, The New York Hospital-Cornell Medical Center Archives, and Biomedical Communications. In addition to his responsibilities at Cornell, he is Visiting Associate Professor, Graduate School of Information and Library Science, Pratt Institute, Brooklyn, New York where he teaches Medical Librarianship. His major emphasis has been on managing change which involves both the assessment of the need for change as well as the process for bringing about and managing change. It also includes managing the implementation of information technology and the change in the educational preparation of librarians for this new environment. His major area of interest is the role of the health sciences librarian in the academic health sciences center.

**RECENT PUBLICATIONS**

**Frisse, M., Braude, R.M., Florence, V., Fuller, S. Informatics and medical libraries: Changing needs and changing roles. Acad. Med.; 70:30-5, 1995.**

**Braude, R.M., Frisse, M., Florence, V., Fuller, S. The organization of the digital library. Acad Med. 70: 286-91, 1995.**

*Clinical Epidemiology*

# Lawrence D. Brown, Ph.D.

## HEALTH POLICY, ECONOMICS AND HEALTH SERVICES RESEARCH

Lawrence Brown, Ph.D. is Professor and Head of the Division of Health Policy and Management at the Columbia University School of Public Health. Dr. Brown is also a member of the National Advisory Committee of the Robert Wood Johnson Foundation's Health Policy Research Scholars Program, the United Hospital Fund's President's Council, and the board of the Community Services Society. A former Senior Fellow at the Brookings Institution for Governmental Studies, Dr. Brown has authored numerous publications, focusing on competitive and regulatory issues in health, on the politics of state and national strategies to achieve affordable universal coverage, and on the used of policy analysis in the policy process. His current research projects include: an assessment of the institutional capacities of the states to pursue health reform, the implications of managed care in Medicaid, the political prospects for universal health coverage for children, patterns of cooperation between managed care plans and academic medical centers, and the diffusion of health policy innovations between the United States and other nations.

**RECENT PUBLICATIONS**

**Brown, L.D. The Politics of Medicare and Health Reform, Then and Now. Health Care Financing Review. 18: 163-168, 1996.**

**Brown, L.D. (with Stevens, B.A) "Expertise Meets Politics: Efforts to Work with the States," in Stephen L. Isaacs and James R. Knickman, eds., To Improve Health and Health Care. San Francisco. Jossey-Bass.pp. 78-96, 1997**

*Clinical Epidemiology*

# Martha L. Bruce, Ph.D., M.P.H.

## BEHAVIORAL SCIENCE, HEALTH PROMOTION AND DISEASE PREVENTION

Martha L. Bruce, Ph.D., M.P.H., is an Associate Professor of Sociology in Psychiatry, Cornell University Medical College. Dr. Bruce was trained in psychiatric epidemiology and medical sociology and is an expert in population-based survey design and sampling procedures. Her research focuses on psychosocial risks factors and outcomes of depression in later life, with a major focus on the longitudinal relationships between depression and functional disability. Both depressive disorders and functional disability are highly prevalent in sub-populations of the elderly. Each is characterized by immense personal suffering and each contributes to the risk of mortality, institutionalization, and dependent living. Dr. Bruce's published work includes epidemiologic analyses of data from community-based samples of elderly adults that affect social and functional factors on incident and recurrent risk of major depression and depressive symptoms, as well as studies of the impact of depression on functional decline and mortality. Dr. Bruce is currently investigating major depression in a representative sample of elderly patients receiving homecare nursing services. The study integrates both clinical and epidemiologic methods in its design and assessment characteristics, and is the first to estimate the prevalence, clinical characteristics, risk factors, and outcomes of diagnosed major depression and subsyndromal in this medically ill and disabled population. Her other studies include an epidemiologic investigation of depressive symptomatology in elderly clients of a "meals-on-wheel" program for the urban poor and longitudinal analyses of the impact of depression on disability in elderly depressed psychiatric patients. As part of this work, Dr. Bruce is also investigating the extent to which depression is recognized and treated in elderly populations and the impact of treatment on longitudinal course. The goal of these studies is to identify potential intervention strategies aimed at risk reduction and modification of outcomes in high risk elderly populations.

**RECENT PUBLICATIONS**

**Bruce M.L. (with McAvay, G.). Epidemiology of Psychiatric Disorders in Late Life. Primary Psychiatry, 5:59-65, 1998.**

**Bruce M.L. (with Meyers, B.S.). Outcomes for antidepressant trials in late-life depression. Psychopharmacology, 33: 701-705, 1997.**

*Clinical Epidemiology*

# Mark A. Callahan, M.D.

## HEALTH POLICY, ECONOMICS AND HEALTH SERVICES RESEARCH

Mark Callahan, M.D. is an Assistant Professor of Medicine at Cornell and Director of Outcomes Research for The New York and Presbyterian Hospital Care Network. His research interests lie in measuring the quality of care provided by hospitals and physicians, and in designing interventions to improve the quality of care. Dr. Callahan directs several multi-hospital studies in the network examining the quality of care delivered to patients treated for acute myocardial infarction, community acquired pneumonia, neonates admitted to Neonatal Intensive Care Units, and is developing a new intervention program for underserved pediatric asthma patients. Dr. Callahan is also co-investigator, along with Dr. Oliver Fein, for the Partnerships for Quality Education (PQE). Under PQE, Dr. Callahan has developed an innovative program for measuring the quality of care provided by residents in their outpatient practices.

**RECENT PUBLICATIONS**

**Callahan, M. (with Grunenbaum, M., Luber, P. et al) Predictors of missed appointments for psychiatric consultations in a primary care clinic. Psychiatric Services. 1996 Vol. 47 No. 8., 1996.**

**Callahan, M. (with Gross, C, and Meie. J.) Will commercial managed care patients accept residents as their primary care providers? Journal of General Internal Medicine, 1998.**

*Clinical Epidemiology*

# Mary E. Charlson, M.D.

## CLINICAL EPIDEMIOLOGY

Mary Charlson, M.D. is a well established investigator with a track record in conducting clinical research trials. In addition her professional affiliation as Chief of General Internal Medicine and the Foley Professor of Medicine, she is also the Program Chairperson for for the Masters Program in Clinical Epidemiology and health Services Research and the Co-Director of the for the federally funded Health Services Research Training Program. As a methodologist and clinical epidemiologist, her own research has focused on the methods of improving prognostic stratification in acute and chronic illness, especially in patients undergoing surgery. She is also an expert in issues using those measures in measurement and methodology of clinical research, and developed the comorbidity index. Some of her projects include: Improving outcome and quality of life after coronary artery bypass graft (CABG) surgery. The principal objective of this randomized trial is to compare the efficacy of two strategies of intraoperative hemodynamic management during cardiopulmonary bypass in preventing perioperative cardiac, cognitive and neurologic morbidity and mortality and postoperative deterioration in patients' quality of life; Improving outcomes in ambulatory patients, predicting patterns of resource utilization, and outcomes in ambulatory patients; Conducting population-based surveys. These surveys serve to document the prevalence of chronic conditions in the community and identifies barriers to care.

**RECENT PUBLICATIONS**

**Charlson, M.E., (with Gold, J.P., Williams-Russo, P.G., Szatrowski, T.P., Peterson, J.C., Pirraglia, P.A., Hartman, G.S., Yao, F.SS, Hollenberg, J.P., Barbut, D., Hayes, J.G,Thomas, S.J., Purcell MH, Mattia S, Gorkin L, Post M, Krieger K, Isom OW). Improvement of outcomes after coronary arterial bypass: A randomized trial comparing intraoperative high vs. Low mean arterial pressure. Journal of Thoracic and Cardiovascular Surgery. 110:1302-14, 1995.**

**Charlson, M.E .(with Hartman ,G.S., Yao, F.S.F, Bruefach, M., Barbut, D., Peterson, J.C., Purcell, M.H., Gold, J.P., Thomas, S.J. and Szatrowski, T.P.). Severity of aortic atheromatous disease diagnosed by transesophageal echocardiography predicts stroke and other outcomes associated with coronary artery bypass grafting surgery: a prospective study. Anesthesia and Analgesia 83: 701-8, 1996.**

*Clinical Epidemiology*

# Oliver T. Fein, M.D.

## HEALTH POLICY, ECONOMICS AND HEALTH SERVICES RESEARCH

Oliver Fein, M.D. is a general internist with interest and experience in health policy. His work has focused on health system delivery reform on both the national and local levels. On the national level, he was a Robert Wood Johnson Health Policy Fellow during 1993-1994, when he worked as a legislative assistant in the office of Senate Democratic Majority Leader, George Mitchell. In this capacity, he was involved with developing policy on health care benefits, graduate medical education, health care quality, public health, medical malpractice, antitrust and remedies and enforcements. On the local level, Dr. Fein has been concerned with access to health care for vulnerable populations and the role of the Academic Health Center. In this regard, he spent 17 years at the Columbia Presbyterian Medical Center developing ambulatory care practices at the Medical Center and in the community. Presently, at Cornell University Medical College, he is involved with developing an academic, integrated delivery system through the New York and Presbyterian Hospital Care Network. Dr. Fein's health services research interests include ambulatory case-mix measurement and risk adjustment. He has also been concerned with different methods of measuring social class and health inequalities. Presently, he is involved with comparing the role of primary care in health system reform in the United States and the United Kingdom. He is currently responsible for the David Rogers Health Policy Colloquium at the New York Hospital-Cornell Medical Center. This weekly seminar brings outstanding visitors in health policy to the Medical Center for presentation and discussion. Over the course of the year, Colloquium participants receive a rich menu of topics in contemporary health policy and politics. The Colloquium serves as an exciting introductory health policy course for fellows enrolled in the Health Services Research fellowship program.

**RECENT PUBLICATIONS**

**Fein, O. The Influence of Socioeconomic Class on Health Status: American and British Research on Health Inequalities. Journal of General Internal Medicine. 10:677-86, 1995.**

**Fein, O. (with S. Matos-Cloke, R. Lantigua.) Hispanic Patients in an Academic Group Practice: Measurement Issues and Comparisons with Non-Hispanics. Journal of Association for Academic Minority Physicians. 7:31-36,1996.**

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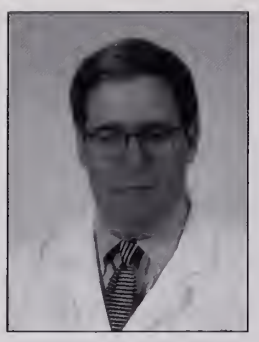


# Joseph J. Fins, M.D.

## MEDICAL ETHICS

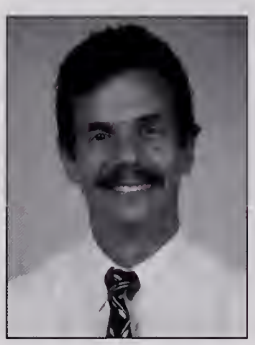
Joseph J. Fins, M.D. is the Director of Medical Ethics at The New York Hospital and Chair of the Hospital's Ethics Committee. He is also an Associate Professor of Medicine and an Assistant Professor of Medicine in Psychiatry at the Weill Medical College of Cornell University. Additional academic appointments include his role as Associate for Medicine at the Hastings Center, and the Physician-Ethicist-in Residence at the HealthCare Chaplaincy in New York City. Dr. Fins is a practicing internist, and teaches medicine and clinical ethics to medical students at the Weill Medical College and housestaff at New York Hospital. A prolific writer, Dr. Fins' has published several articles across on various health-related topics, including the allocation of health care resources, health care reform, economics and medicine, managed care, end-of-life decisions, palliative care, futility, advance directives, the doctor-patient relationship, post-graduate medical education, physician-assisted suicide, brain death, ecosystem health, medical ethics in a pluralistic society, and clinical pragmatism as a method of moral problem-solving for medicine. His editorial responsibilities include the Journal of Pain and Symptom Management, and Cancer Investigation. In 1997, Dr. Fins was appointed to the New York State Attorney General's Commission on Quality of Care at the End of Life.

**RECENT PUBLICATIONS**

**Fins, J.J. Advance directives and SUPPORT. Journal of the American Geriatrics Society. 45: 519-520, 1997.**

**Fins, J.J. ( with Bacchetta M.D., and Miller F.G.). Clinical Pragmatism: A Method of Moral Problem Solving. Kennedy Institute of Ethics Journal. 7: 129-145, 1997.**

*Clinical Epidemiology*



# James P. Hollenberg, M.D.

## MEDICAL INFORMATICS AND DECISION ANALYSIS

James Hollenberg, M.D. is an Associate Professor of Medicine with special interest in the application of decision analytic techniques and artificial intelligence techniques to medicine. He is nationally recognized for his contributions to the theory and practice of decision analysis, and has developed SMLTREE, the most widely used and versatile microcomputer program in the area. Dr. Hollenberg is an expert in decision analysis, and in the use of Markov techniques for exploring transitions in clinical states. His current research involves developing and integrating a sophisticated artificial intelligence program to monitor an operational computerized patient care system. Dr. Hollenberg's primary research interest is medical informatics. He has written many of the clinical information systems in use throughout the New York Hospital-Cornell University Medical College Center.

**Computer Programs:**

Hollenber, J.P. SMLTREE. A program that teaches decision analysis and allows users to construct complex decision trees and Markov processes, 1985.

Hollenberg, J.P. CLIMACS. Clinical Information Management for Ambulatory Care Services. A large scale clinic management system designed to manage all aspects of ambulatory patient care, 1992.

Hollenberg, J.P. INTRAOP. A real time program that manages and analyzes intra-operative information from medical instruments and permits users to chart events, 1992.

**RECENT PUBLICATIONS**

**Hollenberg, J.P. (with Gold, J.P., Charlson, M.E., Williams-Russo, P., Szatrowski, T.P., Peterson, J.C., Pirraglia, P.A., Hartman, G.S., Yao, F.S.F., et al.) Improvement of outcomes after coronary artery bypass: a randomized trial of high versus low arterial pressure. Journal of Thoracic and Cardiovascular Surgery. 110:1302-1314, 1995.**

**Hollenberg, J.P. (with Pirraglia P.A., Williams-Russo, P, Hartman, G.S., Gold, J.P., Yao F.S.F. and Thomas, S.J.). Computerized data collection in the operating room during coronary artery bypass surgery: a comparison to the hand-written anesthesia record. Journal of Cardiothoracic and Vascular Anesthesia. 11(5):545-551, 1997.**

*Clinical Epidemiology*

# Donald S. Kenkel, Ph.D.

## HEALTH POLICY, ECONOMICS AND HEALTH SERVICES RESEARCH

Donald S. Kenkel, Ph.D. is an Associate Professor in the Department of Policy Analysis and Management. His expertise is in the areas of health economics and public sector economics. Much of Dr. Kenkel's research is on the economics of consumer health behavior, including both medical care purchases and health promotion and disease prevention choices made outside of the medical care sector. For the past five years Dr. Kenkel has conducted a series of studies on the economic aspects of alcohol policies, looking at taxing alcohol to prevent alcohol problems.

**RECENT PUBLICATIONS**

**Kenkel, D.S. Self-Insurance and Worksite Alcohol Programs: An Econometric Analysis. Journal of Studies on Alcohol 58:211-219, 1997.**

**Kenkel, D.S. New Estimates of the Optimal Tax on Alcohol. Economic Inquiry 296-319, April 1996.**

*Clinical Epidemiology*

# John M. Kuder, Ph.D.

## HEALTH POLICY, ECONOMICS AND HEALTH SERVICES RESEARCH

John Kuder, Ph.D., is an Associate Professor of Health Economics and Finance. He is also the Director of the Sloan Program in Health Services Administration at Cornell University in Ithaca, New York, and was the Director of the Center for Applied Research at Henry Ford Health Care System in Detroit. Dr. Kuder's research background focuses primarily on the financing of health care, decision making regarding the use of services, and more recently on the impact of managed care systems on Medicaid populations. Dr. Kuder's teaching and studies are on the organization, financing and economics of health services and health insurance from a systems perspective. His work focuses primarily on how public policy shapes the organization and financing of services and how decisions, by consumers and health service providers, are then influenced by these changes. In addition to the use of services, his work concerns issues regarding consumer and physician satisfaction, efficiency, cost, and equity. His is primarily interested in the influence that policy has on vulnerable populations including rural populations, children, the elderly, the poor and the chronically ill. Currently, the majority of his research work in on Managed Care and specifically public managed care programs (Medicaid and Medicare).

**RECENT PUBLICATIONS**

**Kuder, J.M. An Analysis of the Current Health Care Environment for Medical Decision Making: Alternative Concepts and Decision Motivation. Motivation and Emotion. 19:221-226, 1995.**

*Clinical Epidemiology*

# Marks S. Lachs, M.D., M.P.H.

## GERIATRICS, GERONTOLOGY AND CLINICAL EPIDEMIOLOGY

Mark S. Lachs, M.,D., M.P.H. is Associate Professor of Medicine and Co-Chief of the Division of Geriatrics and Gerontology at Cornell Medical College. A prominent physician investigator in the field of elder abuse, Dr. Lachs' research, teaching and clinical experience center on improving the quality of life for older adults. Much of his work involves the epidemiology of elder abuse and neglect, a form of family violence that until recently was unrecognized. His goal is to bring rigorous methodology to this under-studied field. The focus of his research includes the identification of risk factors for reported elder mistreatment and, more recently, the survival of older adults who have experienced mistreatment. This has been accomplished by linking adult protective service (APS) records with an established cohort of community dwelling older adults (one of the National Institute of Aging's established population for epidemiologic studies in the elderly cohorts or (EPESE). Dr. Lachs also has a long-standing interest in health care policy issues and financing in long-term care.

**RECENT PUBLICATIONS**

**Lachs MS, (with Williams CS, O'Brien S, Pillemer KA, Charlson ME) The Mortality of Elder Mistreatment. JAMA. 280 (5):428-432, 1998.**

**Lachs MS (with Ruchlin HS). Is Managed Care Good or Bad For Geriatric Medicine? J Am Geriat Soc 45:123-1127, 1997.**

*Clinical Epidemiology*

# Andrew C. Leon, Ph.D.

## BIOSTATISTICS

Andrew Leon, Ph.D. contributes to the literature in psychometrics and research methodology. He is a co-investigator in the NIMH Collaborative Depression Study and in a NIDA study of suicide and violence. He is on the editorial board of the Journal of Mental Health Policy and Economics. He recently showed empirically that researchers, through their careful selection of the most reliable outcome measures, could reduce the sample size requirements of their proposed studies and, as a consequence, substantially decrease their research costs. He has stressed that researchers balance the clinical meaningfulness of their findings with the statistical significance. This was shown in his manuscript on the use of the effect size to detect differences in treatment response to psychopharmacological agents, for which he received the National Institute of Mental Health New Clinical Drug Evaluation Units Young Investigators' Award. Dr. Leon has written on issues pertaining to changes in mental health economics, focusing on the detection of mental disorders in primary care. He developed screens for detecting mental disorders in primary care which were validated using chance-corrected operating characteristics to evaluate case detection rates. In related work, he considered the problem of false positive screens and discussed fundamental issues of design and analysis in screen development.

**RECENT PUBLICATIONS**

**Leon, A.C. (with Olfson, M., Weissman, M.M., Protera, L,. Sheehan, D.V.). Evaluation of Screens for Mental Disorders in Primary Care: Methodological issues. Psychopharmacology Bulletin. 32:353-361, 1996.**

**Leon, A.C. (with Portera, L., Olfson, M, Weissman, M.M., Kathol, R., Farber, L., Sheehan, D.V,. Pleil, A.M.). False Positive Results: A challenge of Psychiatric Screening in Primary Care. Am J Psychiatry. 154:1462-1464, 1997.**

*Clinical Epidemiology*

# Carol A. Mancuso, M.D.

## CLINICAL EPIDEMIOLOGY

Carol A. Mancuso, M.D. is an internist and clinical epidemiologist, with joint appointments at The New York Hospital-Cornell Medical Center and the Hospital for Special Surgery. As a Robert Wood Johnson Generalist Faculty Scholar and Director of the General Medicine Consultation Service, Dr. Mancuso works closely with members of different Departments at both hospitals and is actively involved in teaching housestaff and medical students. Dr. Mancuso's research interests include chronic diseases, patients' experiences with medical care, and methodological issues in clinical research. Several research initiatives in the area of osteoarthritis focus on ascertaining consensus regarding indications for hip and knee replacements, and patients' expectations and satisfaction with hip replacement. A methodological issue of interest is assessing the validity of relying on patients' recall to assess effectiveness of interventions in cross-sectional studies. An additional major area of interest incorporates a wide variety of issues, including patients' expectations of treatment, prior experiences with medical care, comorbidity, self-efficacy, and access to care. Dr. Mancuso is a Co-Director of the Hospital for Special Surgery Outcomes Unit, a collaboration of health services researchers who assess outcomes of medical and surgical interventions.

**RECENT PUBLICATIONS**

**Mancuso, C.A. (with Charlson, M.E.) Does recollection error threaten the validity of cross-sectional studies of effectiveness? Medical Care. 33: AS77-AS88, 1995.**

**Mancuso, C.A. (with Ranawat, C.S., Esdaile, J.M., JohansonM N.A,. Charlson, M.E). Indications for total hip and total knee arthroplasties: Results of orthopedic surveys. J. Arthroplasty. 11:34-46, 1996.**

*Clinical Epidemiology*

# Charles E. McCulloch, Ph.D.

## BIOSTATISTICS

Charles E. McCulloch is the Chairman of the Department of Statistical Science and the Director of the Statistics Center at Cornell University. He teaches undergraduate and graduate level biostatistics courses, and directs graduate students majoring in statistics and biostatistics and students minoring in a variety of other areas. A Fellow of the American Statistical Association and a member of the International Statistical Institute, Dr. McCulloch has authored many publications on statistics. His other scholarly activity include his roles as Associate Editor for the Journal of the American Statistical Association and the Journal, Biometrics. Dr. McCulloch conducts primary research on the development of statistical methodology for the biological sciences and works closely with other scientists on collaborative research. Funded by the National Science Foundation, his most prominent research area has been generalized linear mixed models. This is an area of strong relevance to longitudinal data analysis and clinical trials.

**RECENT PUBLICATIONS**

**McCulloch, C. E. An introduction to generalized linear mixed models. In Proceedings of the 1996 Kansas State University Conference on Applied Statistics in Agriculture. (G. Milliken and D. Johnson, Eds.) 1-17, 1997.**

**McCulloch, C.E., Paal, B., and Ashdown, S. An optimization approach to apparel sizing. Journal of the Operational Research Society. 49: 492-99, 1998.**

*Clinical Epidemiology*

# Barnett S. Meyers, M.D.

## HEALTH POLICY, ECONOMICS AND HEALTH SERVICES RESEARCH

Barnett Meyers, M.D. is an Associate Professor of Clinical Psychiatry at Cornell University Medical College. Dr. Meyers has served in leadership positions for a number of national professional organizations and is past-president of the American Association for Geriatric Psychiatry. He has spent over fifteen years studying the diagnosis and both acute and long-term treatment of geriatric mood disorders. This work has produced over 75 scientific publications. Dr. Meyers' scientific activities have been supported by two career development awards from the National Institute of Mental Health. He is currently principal investigator of a controlled study of prevention of relapses in late-life delusional depression and a mental health services research program grant, both of which are funded by the National Institute of Mental Health.

**RECENT PUBLICATIONS**

**Meyers BS (with Moline, M.D.). The Role of Estrogen in Late-Life Depression: Opportunities and Barriers to Research. Psychopharm Bull. 33 (2): 289-291, 1997.**

**Meyers, B.S. Telling patients they have Alzheimer's Disease. Brit Med Journ. 314: 321-322, 1997.**

*Clinical Epidemiology*

# Stephen A. Paget, M.D.

## HEALTH POLICY, ECONOMICS AND HEALTH SERVICES RESEARCH

Stephen Paget, M.D. is the Joseph P. Routh Professor of Medicine, Cornell University Medical College and Physician-in-Chief at Hospital for Special Surgery. Dr. Paget's research interests include the identification of effective and safe treatments for systemic vasculitides such as giant cell arteritis, which resulted in the conduct of a randomized double blinded trial to assess the clinical effectiveness of Methotrexate in the treatment of giant cell arteritis. He was also Co-principal investigator in a randomized controlled double-blinded study assessing the effectiveness of salmon calcitonin in preventing osteoporosis in steroid-treated patients with giant cell arteritis and polymyalgia rheumatica that has demonstrated the clinical effectiveness of calcium supplementation as opposed to calcitonin. Dr. Paget is also studying the association of the Whipple's organism (tropheryma whippeli) as a causative agent in seronegative arthritis.

**RECENT PUBLICATIONS**

**Paget, S.A. (with Healey, J.H., Williams-Russo, P, et al.) A randomized trial of salmon calcitonin to prevent bone loss in corticosteroid-treated temporal arteritis and polymyalgia rheumatica. Cal Tis In. 58:73-80, 1996.**

**Paget, S.A. (with Russell, L.A.). Immune system health and disorders over life phases: In Textbook of Women's Health, Lila A. Wallis. Ed. Lippincott-Raven, Philadelphia, PA, p. 481-493, 1998.**

*Clinical Epidemiology*

# Margaret G. E. Peterson, Ph. D.

## BIOSTATISTICS

Margaret Peterson, Ph.D. is a Research Statistician, with appointments at Hospital for Special Surgery and at Cornell University Medical College. Her research focuses on the use of statistics in medical research and the evaluation of education and teaching programs. Dr. Peterson has worked extensively in the development and evaluation of computer-based teaching programs both for health professionals and for patients. Other projects have involved the use of computers by the general public and barriers to acceptance of educational methods including telephone access. She has investigated methods of delivering information to physicians simulating progression of events with time. In addition, she has written several computer programs for Apple computers for use in statistics courses and by other health professionals. She coordinated the development of a major Rheumatology database at the University of Connecticut. Dr. Peterson pursues research in two main areas. (1) The extraction and comparison of data from existing databases. (2) The collection and analysis of patient outcome data in orthopaedic and musculo-skeletal health problems. Her work with existing databases has led to collaborations on comparisons of geographic variations in elective surgery and the use of Medicare databases to select random samples. She has also collaborated on the development and evaluation of a tool to measure outcomes in the treatment of painful shoulders. She is currently involved in trials to better outcomes for hip fracture patients, of the clinical effectiveness of methotrexate in giant cell arteritis, of the outcome of treatments for shoulder pain and in the analysis of survey responses from Medicare beneficiaries. She teaches statistics, questionnaire design, coding, database design, and the use of computers in statistics to fellows at the Hospital for Special Surgery and to those enrolled in the Clinical Epidemiology and Health Services Research Masters Program.

**RECENT PUBLICATIONS**

**Peterson, M.G.E. (with Hollenberg, J.P., Szatrowski, T.P., Johanson, N.A., Mancuso, C.A., Charlson, M.EE) Geographic Variation in the Rates of Elective Total Hip and Knee Arthroplasties among Medicare Beneficiaries in the United States. Journal of Bone Joint Surgery. 74-A:1530-1539, 1992.**

**Peterson, M.G.E. (with L'Insalata, J.C,. Warren, R.F,. Cohen, S.B., Alchek, D.W.) A Self-Administered Questionnaire for Assessment of Shoulder Symptoms and Function. Journal of Bone Joint Surgery. 79-A:738-748, 1997.**

*Clinical Epidemiology*

# Karl Pillemer, Ph.D.

## GERIATRICS AND GERONTOLOGY

Karl Pillemer, Ph.D. is a sociologist whose research focuses on social gerontology. He is an Associate Professor of Human Development at Cornell University and the co-director of the Cornell Applied Gerontology Research Institute, a federally-funded program that focuses on applied research and intervention studies which are designed to promote the social integration of older persons, particularly in the form of social support and involvement in meaningful roles. One of his major research interests is in the family relationships of the elderly, including the effects of relationships with adult children on elderly parents' well-being. He has also extensively studied issues of family caregiving to impaired elderly relatives. In two longitudinal studies, funded by NIMH and NIA, he is examining changes over time in caregivers' social networks after their relative is diagnosed with a major medical illness as well as ways in which changes in the network affect caregivers' psychological well-being and sense of burden. Over the past decade, Dr. Pillemer has also conducted a program of research and intervention studies on nursing homes. Other areas of academic interest include abuse of elderly persons, both in nursing home and in domestic settings, and social policy and aging.

**RECENT PUBLICATIONS**

**Pillemer, K. (with J. Jill Suitor). It Takes One to Help One: Effects of Status Similarity on Well-Being of Caregivers. Journal of Gerontology, 51B: S250-257, 1996.**

**Pillemer, K. Solving the Frontline Crisis in Long-Term Care. Cambridge, MA: Frontline Publishing Corporation, 1996.**

*Clinical Epidemiology*

# Laura Robbins, D.S.W.

## BEHAVIORAL SCIENCE, HEALTH PROMOTION AND DISEASE PREVENTION

Laura Robbins, DSW is the Director of the Education Division at the Hospital for Special Surgery and Associate Director of the Education, Epidemiology and Health Services Research component of the Cornell Arthritis and Musculoskeletal Disease Center. Her research focuses on barriers to utilization and access to health care services. She is particularly interested in culturally determined health beliefs and behaviors that determine the use of health services and social support programs. Currently, she is investigating service utilization in two disease-specific areas, osteoporosis and lupus. The target populations studied are the Latino and Chinese- American Communities. While evaluating levels of knowledge and health beliefs in the prevention of these diseases, Dr. Robbins is evaluating how knowledge and beliefs mediate utilization of existing services. Her study in osteoporosis aims to document the prevalence of this disease in acculturated Latina women. The second study is a randomized control study of a psycho-education program designed to increase functional outcomes through a peer support and education program. The program, available in English and Spanish, consists of didactic education sessions as well as a telephone peer support component. Additionally, inquiry is also ongoing in the area of pediatric care for underserved children with musculoskeletal conditions. This study focuses on access to health care services, surveying parents of children who participated in a community-based musculoskeletal screening program in which over 10,000 children have been screened. This program has incorporated a primary care component which involves the coordination of all pediatric services. The study, which originally focused on Latino and African-American children, has now been expanded in the Chinese-American community.

**RECENT PUBLICATIONS**


**Robbins, L. Social and Cultural Assessment. In: S Wegener, B Belza, E Gall (Eds). Primer Clinical Care in Rheumatic Diseases. The American College of Rheumatology, 1996.**

**Robbins L. Patient Education: In: J Klippel, C Weyand, R Wortmann (Eds). Primer on Rheumatic Diseases, 11th Edition, National Arthritis Foundation, 1997.**


*Clinical Epidemiology*

# Eunice Rodriguez, Dr. PH

## HEALTH POLICY, ECONOMICS AND HEALTH SERVICES RESEARCH

Eunice Rodriguez, Dr.PH, is an Assistant Professor in the Department of Policy Analysis and Management at Cornell University, and teaches a graduate course on health status measurement and outcomes evaluation. Dr. Rodriguez has extensive health services research experience in minority communities, and is currently working on a study to assess the role of formal and informal mechanisms of social support to predict mental and overall health status of African-Americans. Preliminary results of her analysis of the panel data of the National Survey of Families and Households indicates that entitlement programs could be important in ameliorating the impact of joblessness on depression for other than solely economic reasons. She is also developing appropriate outcomes measurements for hospice care, and conducting an evaluation of injury control programs in public housing. Funded by the Statewide Research/Extension Program, this is a collaborative research project which examines injury prevention programs administered in public housing facilities. This study brought together university researchers, public housing administrators and insurance company personnel to focus on strategies aimed at increasing the safety of public housing residents and improving the lives of limited resource families.

**RECENT PUBLICATIONS**


**Rodriguez, E., Lasch, K., Mead, J.P. The Potential Role of Unemployment Benefits in Shaping the Mental Health Impact of Unemployment. International Journal of Health Services 27: 601-623, 1997.**

**Rodriguez, E. and Mead, J.P. A Theory-oriented Approach to the Evaluation of Community Based Primary Care Programs. Evaluation and Program Planning. Vol. 20: 217-224, 1997.**


*Clinical Epidemiology*

# Hirsch S. Ruchlin, Ph.D.

## HEALTH POLICY, ECONOMICS AND HEALTH SERVICES RESEARCH

Hirsch Ruchlin, Ph.D., is a Professor of Economics in the Departments of Public Health and Medicine. He has had over 20 years experience designing and conducting economic analyses in the health care field. His current research interests encompass: (a) the organization and delivery of services within both the acute and long-term care sectors of the U.S. health care system and (b) cost-benefit and cost-effectiveness analyses of various medical interventions. He has recently completed a study of the determinants of health promotion and disease prevention among older adults. He is currently working on a cost-benefit analysis of a randomized trial of self-efficacy and high-intensity strength training to improve postoperative rehabilitation of hip fracture patients, and is conducting cost-effectiveness analyses in the areas of the treatment of head and neck cancer, and prostate cancer. Dr. Ruchlin has been an economic consultant to various federal, state, and local government agencies, and to private sector research groups. He is involved with courses given to first and fourth year medical students, being a seminar leader on topics involving physician and hospital reimbursement, managed care, and physician work-force requirements. Within this program, he teaches courses that provide an overview of current health services research, health economics, and cost-benefit/cost-effectiveness analyses.

**RECENT PUBLICATIONS**

**Ruchlin, H.S. (with Mattia, S., Morris, J.M.) Resident medical care utilization patients in continuing care retirement communities. Health Care Review. 14:183-188, 1993.**

**Ruchlin, H.S. Prevalence and Correlates of alcohol use among older adults. Preventive Medicine 26: 651-657, 1997.**

*Clinical Epidemiology*

# Carol Storey-Johnson, M.D.

## INFORMATION SYSTEMS AND EDUCATION

*Carol Storey-Johnson, M.D.*, an Associate Professor of Clinical Medicine, is the Associate Director of the Office of Curriculum and Educational Development at the Medical College. In this position she is involved in course planning, implementation and evaluation of the new integrated curriculum for the Medical College. She also directs the Medical Clinical Education Unit in the Division of General Internal Medicine and the Medicine, Patients, and Society Course Curriculum for first year medical students. Dr. Storey-Johnson has developed education programs for the primary care medical residency track, and the ambulatory medical student block rotations, and is now in charge of developing a new curriculum for the first two years of medical student education that will provide interdisciplinary training in the development of clinical skills. A graduate of the Stanford Faculty Development Program, Dr. Storey-Johnson teaches the faculty and fellows how to teach, using Stanford techniques. She also conducts program evaluations to discern whether learning objectives and content are consistent with projected educational outcomes.

**RECENT PUBLICATIONS**

**Storey-Johnson, C.L. (with Winters, R.A., Helfott, D., Murray, H.W.). HIV infection and bacteremic meningococceal pneumonia. J. Infect. Dis. 183: 1390-91, 1991.**

*Clinical Epidemiology*

# Ted P. Szatrowski, M.D.

## BIOSTATISTICS

Ted P. Szatrowski, M.D. is an Associate Professor of Medicine. A board certified Hematologist and Oncologist, Dr. Szatrowski also chairs the Cancer and Leukemia Group B, a multi-center clinical trial. He is also a principal Biostatistician at Cornell University Medical College. Dr. Szatrowski is interested in the design and conduct of efficient clinical trials, primarily to investigate and develop novel treatments for hematologic malignancies. Recent efforts have included the following: the assessment of the activity of an immunoconjugate, anti-B4-blocked ricin, which has the potential to deliver the powerful cytotoxin ricin to CD19-positive acute lymphoblastic leukemia cells in a highly specific manner; the testing of recombinant humanized (anti-CD33) monoclonal antibody, HuM195, as therapy for minimal residual disease in patients with acute myeloid leukemia; the evaluation of combination therapy consisting of recombinant interferon-( and the differentiating agent cytarabine for patients with chronic myeloid leukemia. Considerable effort is also devoted to the design and analysis of clinical trials at the medical center outside the anti-neoplastic realm, including those asking questions in coronary artery bypass surgery, rheumatologic therapeutics, prothrombotic states, and orthopedic surgery. The development and validation of measures of outcome applicable to all branches of clinical medicine has been a valuable outgrowth of these trials.

**RECENT PUBLICATIONS**


**Szatrowski, T.P. The chronic Leukemias. In: Conn's Current Therapy, 1995.**

**Szatrowski, T.P. (with Stock, W., Westbrook, C.A., Peterson, B., Arthur, D.C., Silver, R.T., Sher, D.A., Wu, D., LeBeau, M.M., Schiffer, C.A., Bloomfield, C.D.) Value of molecular monitoring during the treatment of chronic myelogenous leukemia: A Cancer and Leukemia Group B study. J. Clin. Oncol. 15:26-36, 1997.**


*Clinical Epidemiology*

# William M.K. Trochim, Ph.D.

## HEALTH POLICY, ECONOMICS AND HEALTH SERVICES RESEARCH

William Trochim, Ph.D., is a Professor in the Department of Human Service Studies at Cornell University. Dr. Trochim is a leader in the field of program evaluation; he is a prolific writer on the subject, and he currently sits on the American Board of Evaluation. A social research methodologist by profession, his fields of expertise include human development, education, and epidemiology. Dr. Trochim is best known for his work on the regression-discontinuity quasi-experimental method, a high-validity alternative to the randomized trial in cases where it is unethical or impractical to randomly assign persons to groups. Dr. Trochim is also noted for his work on mapping ideas to group processes and the application of this technique to the evaluation and program planning process.

**RECENT PUBLICATIONS**


**Trochim, W. M.K. (and Cappeleri, J.C.) Ethical and scientific features of cutoff-based designs of clinical trials: A simulation study. Medical Decision Making 4:387-394, 1995.**

**Trochim, W.M.K, (and McLinden, D.J.). From Puzzles to Problems: Assessing the Impact of Education in a Business Context with Concept Mapping and Pattern Matching. In J. Phillips (Ed.), Return on investment in human resource development: Cases on the economic benefits of HRD - Volume 2. Alexandria, VA: American Society for Training and Development, 1997.**


*Clinical Epidemiology*

# Pamela G. Williams-Russo, M.D., M.P.H.

## CLINICAL EPIDEMIOLOGY

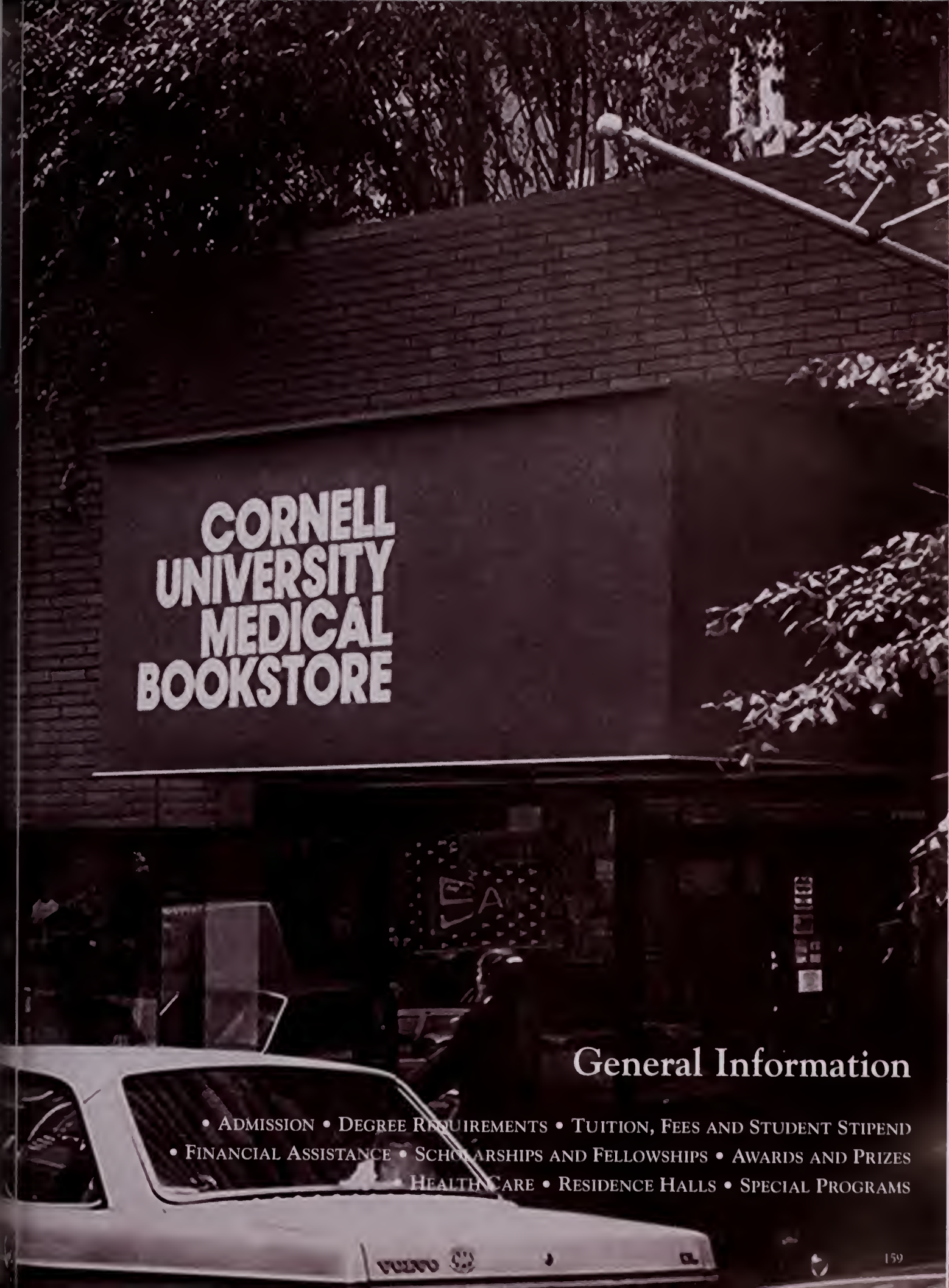
Pamela Williams-Russo, M.D., M.P.H. is an Associate Professor of Medicine with a joint appointment in the Divisions of General Medicine and Rheumatology. She is the Program Director for the Masters Program in Clinical Epidemiology and Health Services Research and the Director of the Hospital for Special Surgery Outcomes Unit. She is a clinical epidemiologist with extensive experience designing, conducting, and analyzing prospective randomized clinical trials focusing on interventions to affect outcomes of importance to both patients and clinicians. Her methodological research interests include development of techniques to determine clinically important differences in results; development of scales to measure functional status outcomes; and longitudinal assessment of change in functional status. Specific clinical research areas includes cognitive function and dementia, perioperative outcomes, depression and comorbid medical illness, and geriatrics. Dr. Williams-Russo serves as clinical epidemiologist on several multidisciplinary research teams at Cornell, providing expertise in study methodology and analysis. These teams include the Geriatric Mood Disorder Clinical Research Center as Director of the Medical Core. She serves as Program Co-Director of a Health Services Research Fellowship program and has major responsibility for day-to-day management of the Fellowship program. She teaches in a variety of ambulatory settings, conferences, and didactic courses, and serves as research mentor for medical students, residents, fellows, and faculty.

**RECENT PUBLICATIONS**


**Williams-Russo, P.G. (with Sharrock, N.E., Mattis, S., Szatrowski, T.P. and Charlson, M.E.) Cognitive effects after epidural versus general anesthesia in older adults: a randomized trial. JAMA 274:44-50, 1995.**

**Williams-Russo, P. (with Haas, S., Sharrock, N.E., Charlson, M.E., Heim, L.) Thromboembolism after TKR: Epidural vs. General Anesthesia, Clin. Orth. Rel. Res. 331:199-208, 1996.**


*Clinical Epidemiology*




# General Information

• Admission • Degree Requirements • Tuition, Fees and Student Stipend
• Financial Assistance • Scholarships and Fellowships • Awards and Prizes
• Health Care • Residence Halls • Special Programs

# Admission

## APPLICATIONS

Applications to the Weill Graduate School of Medical Sciences of Cornell University are accepted for the degree of Doctor of Philosophy and, in the case of the Program in Clinical Epidemiology and Health Services Research, for the degree of Master of Science. An applicant must (1) have a baccalaureate degree or equivalent from a college or university of recognized standing, (2) have adequate preparation in the chosen field of study, and (3) show promise of ability to pursue advanced study and research, as judged by his or her previous record.

Students are admitted to one of the following programs: *Biochemistry & Structural Biology; Cell Biology & Genetics; Immunology; Molecular Biology; Neuroscience; Pharmacology; Physiology, Biophysics and Molecular Medicine, and Clinical Epidemiology & Health Services Research*. However, the initial affiliation with a program is far from rigid. For example, a student, after developing an awareness of the variety of research projects available for training, may change programs, provided the student is in good standing in his or her original program. Program transfers are most easily accommodated during the first year of graduate study in order that the student may complete the required coursework of his or her new program before the Admission to Candidacy Examination held at the end of the second academic year.

Inquiries concerning graduate study should be addressed to the Associate Dean of the Graduate School of Medical Sciences, 445 East 69th Street, New York, NY 10021 [Telephone: (212) 746-6565; Fax (212) 746-8906; E-mail address: gsms@mail.med.cornell.edu].

All application materials must be completed and returned to:

Office of the Graduate School of Medical Sciences
Olin Hall 412
445 East 69th Street
New York, NY 10021

together with (1) official transcripts of records from all colleges and universities attended, (2) a statement of purpose of graduate study, and (3) two letters of recommendation from individuals in academic positions who know the applicant professionally. In addition, scores from the Graduate Record Examinations (GRE) are required to aid in the evaluation of an applicant. Application for taking the Aptitude (Verbal, Quantitative, and Analytical) Test and the Advanced Test of the GRE must be made directly to the Educational Testing Service, Graduate Record Examinations, P.O. Box 6000, Princeton, NJ 08541-6000. Students whose native language is not English are required to take the Test of English as a Foreign Language (TOEFL). Application for this test must be made to: Test of English as a Foreign Language, P.O. Box 6151, Princeton, NJ 08541-6151. The proper Institution Code Number to use in the GRE or TOEFL application for the Weill Graduate School of Medical Sciences of Cornell University is R 2119.

All applications and credentials for September admissions, including official transcripts of records from all colleges and universities attended, must be postmarked by the deadline date of December 31. Because GRE scores are an important part of the application, it is of decided advantage to the applicant to submit these scores by the December 31st deadline. A nonrefundable **application fee** of $50 must accompany the application for admission.

### Admissions Process

The completed application and all supporting documents are initially screened by the credentials committee of the Program of Study to which the student is applying. Applicants considered potentially acceptable will be notified and invited to attend the graduate school recruitment days held in February for two days of program orientation, personal interviews, and meeting fellow candidates, current graduate students, faculty, and the City of New York in a relaxed atmosphere. Candidates approved by each Program are

forwarded to the Dean for final decision. A student is formally notified of acceptance for study in the Weill Graduate School of Medical Sciences of Cornell University by a letter from the Dean. An applicant accepted for admission is requested to inform the Graduate School promptly of her or his plan to either accept or reject the offer of admission.

It is the policy of Cornell University to actively support equality of educational and employment opportunity. No person shall be denied admission to any educational program or activity or be denied employment on the basis of any legally prohibited discrimination involving, but not limited to, such factors as race, color, creed, religion, national or ethnic origin, sex, age, or handicap. Admission policies are also in conformity with the policy of New York State with regard to the American ideal of equality of opportunity as embodied in the Education Practices Act.

## Special Students

Special students are students who are not degree candidates in the Weill Graduate School of Medical Sciences of Cornell University and who are given permission by the Dean or Associate Dean to take courses and/or perform research in the Graduate School. To obtain credits for work performed, special students must be degree candidates at other institutions. Their activities at Cornell must be essential to their degree programs in studies not offered by the institutions in which they are matriculated as degree candidates, as certified by their institution. Enrollment as a special student is not intended as preparation for admission to degree programs at Cornell or elsewhere.

Special students receiving credit are accepted only with the approval of the appropriate Program Chairperson. Such students must demonstrate special qualifications in terms of preparation and ability. They must register with the Weill Graduate School of Medical Sciences of Cornell University and are required to pay all tuition and fees. Tuition is computed on the basis of the ratio of hours occupied by lectures and/or laboratory activities to the total hours of instruction for the academic year (33 weeks of 40 hours/week). There is a registration fee of $50.

# Degree Requirements

## The Special Committee

General degree requirements of the Graduate School of Medical Sciences are minimal in order to give maximum flexibility in choosing a desirable program of study. The student's program of study is determined with the direction of a Special Committee, consisting of at least three faculty members chosen by the student that best fit his or her area of research interest. At least one member of the committee must represent a program different from the candidate's major program. Satisfactory progress toward a degree is judged solely by the committee rather than by standards imposed by the Graduate School of Medical Sciences. There are no regulations from the Weill Graduate School of Medical Sciences of Cornell University governing the specific content of instruction, courses, or grades to which the Special Committee must subscribe, except those imposed by the programs. The committee is primarily responsible for the candidate's development as an independent scholar and scientist.

The major sponsor (thesis advisor) usually advises the student concerning the selection of other committee members. Members may agree to serve until the candidate has had the opportunity to become acquainted with areas of research in the programs of his or her choice. On selection of a thesis project, a permanent Special Committee is formed, the membership of which can be changed during the thesis project with approval of the

Program Chairperson or Director. Members of the Special Committee decide on the student's program of study and research. They judge whether progress toward a degree is satisfactory, and they prepare term reports on the candidate for submission to the Dean. The members of the committee serve on all of the candidate's examining committees and they approve the thesis. The formation of a permanent Special Committee requires the submission by the student of a Nomination of Special Committee form to the Graduate School Office. The Nomination of Special Committee form must be on file to schedule the Admission-to-Doctoral Candidacy Examination.

## Registration and Course Grades

At the beginning of each term, students are required to register with the Graduate School Office by filing a registration form indicating all courses they will take. A fee of $10 is charged for late registration. All courses for which the student registers for credit will be entered in the official transcript record. Grades of graduate students are reported as: Honors (A equivalent), High Pass (B equivalent), Low Pass (C equivalent), Fail (F equivalent), Incomplete (I), Absent (Abs), Officially Withdrawn (W), or Audit (Aud). A grade of Absent cannot be changed later than one term following the term in which the course was taken. Registration for the summer term is required of graduate students who will be engaged in research.

## Residence

The Weill Graduate School of Medical Sciences of Cornell University regards study in residence as essential. Each candidate for an advanced degree is expected to complete the residence requirements with reasonable continuity. A student must register each term from the time of initial registration in the Graduate School until the student either withdraws or completes a degree (unless a leave of absence has been granted). Full-time study for one-half academic year with satisfactory accomplishment constitutes one residence unit. Two units of residence are the minimal requirement for the masters degree and six units are the minimum for the doctoral degree. However, the time necessary to obtain the degree generally exceeds the minimal requirements. Currently, the average time to achieve the Ph.D. degree is five to six years. A candidate for the Ph.D. degree must spend two of the last four units of required residence in successive terms on the New York City or the Ithaca campus of Cornell University. No more than seven years may intervene between the time of first registration and the completion of all requirements for the doctoral degree. A student must complete all requirements for the master's degree within four years.

Part-time graduate study is strongly discouraged. Requests for part-time study must be approved by the Executive Committee of the Graduate School. If permission is granted for part-time study, the student must be in residence at least half-time.

## Transfer of Residence Credit

No residence credit will be granted for study outside the Graduate School of Medical Sciences to fulfill the requirements of the M.S. degree. No commitment can be made about granting residence credit toward the Ph.D. requirements for previous study in another graduate school until after the candidate has entered into residence at the Graduate School of Medical Sciences. At that time, the student's Special Committee may recommend acceptance of study outside the Graduate School of Medical Sciences to the Program Director and Associate Dean, who will jointly determine the number of residence units to be awarded. No credit can be transferred for study undertaken as an undergraduate or as a special student even in courses designed for graduate students.

A student who has satisfactorily completed two or more academic years of study toward the M.D. degree at Weill Medical College of Cornell University, or another accredited

medical school in the United States with a curriculum equivalent to that of the Weill Medical College of Cornell University, may transfer a maximum of two units of residence credit after passing an evaluation examination administered by a committee appointed by the Dean of the Graduate School of Medical Sciences.

## Summer Research

Registration is required for the summer research term whether or not this effort is credited toward residence unit accumulation. Students registered for summer research may pay prorated tuition if they are obtaining residence credit. A degree candidate is eligible for no more than two residence units in any period of twelve consecutive months.

## Study *In Absentia*

A candidate for the degree of Doctor of Philosophy may petition for permission to earn residence units for study away from Cornell University while regularly registered in the Graduate School of Medical Sciences. A candidate to whom this privilege has been granted must register as a Candidate *In Absentia* and may work temporarily under the immediate supervision of an individual designated by the Special Committee. An *In Absentia* student's thesis research will continue to be directed by the Special Committee. No more than two residence units may be earned *in absentia* toward fulfillment of the minimal residence requirements for the Ph.D. degree.

## Leave of Absence

A candidate who finds it necessary to interrupt the continuity of his or her residence must petition the Dean for an official leave of absence. This written petition must specify the term of absence, state the reason for the requested leave of absence, and be approved by the student's major sponsor.

## Candidacy for Degree Only

A graduate student who has fulfilled all degree requirements, with the exception of the final thesis submission, and is no longer a full-time student, is granted Candidate for Degree Only status, which remains in effect until graduation. Degree conferral takes place three times per year, January, May, and August, with the May commencement held jointly with M.D. degree graduates of Weill Medical College of Cornell University.

## Examinations

Three examinations are required by the Weill Graduate School of Medical Sciences of Cornell University: (1) Examination for Admission to Doctoral Candidacy, (2) Final Examination for the M.S. degree and (3) Final Examination for the Ph.D. degree. M.S. and Ph.D. Examinations are administered by an Examining Committee consisting of a chairperson appointed by the Dean, the members of the candidate's Special Committee and one additional member from outside the student's Program of Study who is selected from either the Faculty of the Graduate School of Medical Sciences or from another institution. The Admission to Doctoral Candidacy Examination is administered independently by each program, with attendant separate requirements. In addition to these examinations, the Program may require a qualifying examination as part of its evaluation of the candidate after two units of residence have been completed.

For the M.S. degree: The Final Examination may be oral or both oral and written.

For the Ph.D. degree: The Admission to Doctoral Candidacy Examination is both oral and written and certifies that the student is eligible to present a thesis to the Graduate

School of Medical Sciences. The examination should be taken after course work is largely finished but before significant thesis research has begun. Accordingly, the usual examination time will be at the end of the second year of residence. The examination may not be taken until two units of residence credit have been accumulated, and a minimum of two units of residence credit is required after passing this examination before the final examination can be scheduled. The final examination for the Ph.D. degree is an oral defense of the candidate's thesis. It must be passed within four years after completion of the required residence units, or within seven years from the date of first registration, whichever is earlier.

### Thesis

A principal requirement for both the M.S. and the Ph.D. degrees is the presentation of a thesis constituting an original contribution to the body of scientific research. Ordinarily, the thesis is written on a research topic in the candidate's major field of study, under the direction of the chairperson of his or her Special Committee. The time between the thesis defense and submission of the thesis in its final form is limited to 60 days. The Ph.D. thesis will be published in abstract and recorded on microfilm.

# Tuition, Fees, and Student Stipend

### Tuition and Stipend

All students accepted to Ph.D. degree-granting programs are awarded a full tuition scholarship of $19,215 per annum for 1998-99, which includes all tuition, tuition fees, and health insurance costs. In addition to a full tuition scholarship, a generous graduate student stipend of $22,000 per annum is awarded to each full-time student.

Tuition for a full-time student matriculated in the Masters Degree Program in Clinical Epidemiology and Health Services Research is $21,000 for the entire program. However, students may matriculate and pay tuition on a per credit hour basis (currently $700/credit hour). Tuition includes fees for matriculation, graduation, and miscellaneous thesis expenses.

### Other Fees

**In Absentia.** A student registered *in absentia* pays a fee of $200 each term (2 terms per annum).

**Leave of Absence.** Students on leave of absence will be required to pay an active-file fee of $200 per term, up to a maximum of six terms that they are not registered with the Graduate School. This fee will not be subject to finance charges but must be paid before the student can receive an advanced degree. Petition for waiver of this fee will be considered for students who have not completed the required number of residence units. For students on leave of absence, the student health plan will remain in force for 30 days following commencement of the leave.

**Candidacy for Degree Only**. A student who registers as a Candidate for Degree Only pays a one-time fee of $35.

Any individual who owes money to the University will not be allowed to register at the University, receive a transcript record, have academic credits certified, be granted a leave of absence, have a degree conferred, or be eligible for health services and subsidized housing. The amount, time, and manner of payment of tuition, fees, or other charges may be changed at any time without notice.

# Financial Assistance

Students who wish to apply for a Stafford Student Loan or other Federal assistance are required to submit a Free Application for Federal Student Aid (FAFSA) for an estimate of financial need. Application forms can be obtained from the Graduate School Office. Limited financial assistance in the form of a student loan is available from the Graduate School to qualified applicants. Students are encouraged to apply for competitive predoctoral fellowships available from sources such as the National Science Foundation, the National Research Council, and the Howard Hughes Medical Institute. Information about these fellowships may be obtained directly from the Graduate School Office. Students who are awarded competitive fellowships will receive an additional $1,000 to be used for books and laboratory expenses.

New York State residents are also eligible for several predoctoral fellowships. Application forms may be obtained from Graduate School or the New York Higher Education Services Corporation, Student Financial Aid Section, Tower Building, Empire State Plaza, Albany, NY 12255.

# Scholarships and Fellowships

Full fellowships are available for graduate students. Recipients become Ph.D. Fellows and are awarded a full tuition scholarships and stipend support. Scholarships and fellowships are administered by the Office of the Dean of the Graduate School of Medical Sciences.

**The Vincent Astor Scholarship Fund.** The generous gift by the Vincent Astor Foundation to the Graduate School of Medical Sciences and to the Medical College. Allocation of these funds for graduate students is made at the discretion of the Dean of the Graduate School of Medical Sciences.

**The Harry E. Gould, Sr., Medical and Graduate Student Scholarship.** This fund was established by Mr. Gould's son, Harry E. Gould, Jr., in memory of his father, a prominent business and civic leader in the City of New York who had a long-standing interest in medicine. The income from this endowment provides financial assistance for students of the Medical College and Graduate School of Medical Sciences.

**The Frank L. Horsfall, Jr., Fellowships** are derived from income generated by the Frank L. Horsfall, Jr. Fund and are awarded each year to two outstanding students sponsored by faculty members of the Sloan-Kettering Institute.

**The Shirley L. Marshak Fellowship** is funded by income derived from the Shirley L. Marshak Trust for Charities. The fellowship has been designated for award to a student of the Graduate School of Medical Sciences who is engaged in biomedical research.

**The Avon Foundation Summer Research Program.** The Avon Foundation has granted funding for a program which provides minority college students with summer research opportunities in laboratories of Weill Medical College of Cornell University and the Sloan-Kettering Institute. The aim of the program is to foster an interest in biomedical research in minority students at all college levels. The program provides a two-month stipend and subsidized housing for qualified students.

**DeCamp Tri-Institutional Neuroscience Fund.** Through the generosity of the DeCamp Foundation, a fund has been established to promote neuroscience activities at the Weill Medical College of Cornell University, The Rockefeller University, and the Sloan-Kettering Institute. The gift supports an annual research symposium and graduate student and postdoctoral fellow research dinners.

# Awards and Prizes

**The Julian R. Rachele Prize.** The income of a fund established by Dr. Julian R. Rachele, former Dean of the Cornell University Graduate School of Medical Sciences, provides for an annual prize to be awarded to a candidate for the Ph.D. degree for a research paper of which the candidate is the sole or the senior author.

**The Vincent duVigneaud Prizes, Awards of Excellence, and First Year Award** for the presentation of outstanding papers by students of the Cornell University Graduate School of Medical Sciences at the Annual Vincent duVigneaud Memorial Research Symposium.

# Health Care

The Graduate School is dedicated to providing the finest medical care to students. Prior to matriculation, students must have a general health examination, which includes a physical examination, chest x-ray, and basic laboratory tests, performed by their personal physician with the results forwarded to the Student Health Service. All full-time students enrolled in one of the Ph.D. degree-granting programs are covered by a comprehensive health plan. This includes access to Student Health Services, New York-Presbyterian Hospital clinics, and physician referrals. Major-medical coverage for students and for eligible dependents is also available.

# Residence Halls

**Sloan House,** located at 1233 York Avenue between 66th and 67th Streets, contains 33 studio and 29 one-bedroom apartments that are available to graduate students. Single occupancy of studio apartments and double occupancy of one-bedroom apartments are permitted. All apartments are air-conditioned, fully furnished, and have an outdoor balcony terrace. Building amenities include laundry facilities, front door security, easy access to graduate faculty laboratories at Cornell and SKI, and a new lounge for social relaxation in an quiet upscale setting. Pets are allowed subject to housing restrictions.

**Jacob S. Lasdon House,** an apartment residence located at 420 East Seventieth Street between York and 1st Avenues, contains studio, one-bedroom, and two-bedroom apartments for graduate students, medical students, and postdoctoral fellows. Apartments are fully furnished, include kitchens, and are centrally air conditioned. Building amenities include laundry facilities, front door security, recreation room, and an outdoor terrace. These apartments are available as roommate shares or family housing only. Pets are not permitted.

· **303 E. 71st Street** is an apartment building located between 1st and 2nd Avenues for graduate students only. One-and two-bedroom furnished apartments are available for double occupancy or family housing. Pets are allowed subject to housing restrictions.

**Livingston-Farrand Apartments,** located on E. 69th street between York and 1st Avenues, contain furnished studio, one-bedroom, and two-bedroom apartments with kitchen facilities. These apartments are available for families and for upper-class medical and graduate students wishing single occupancy accommodations. Pets are not permitted.

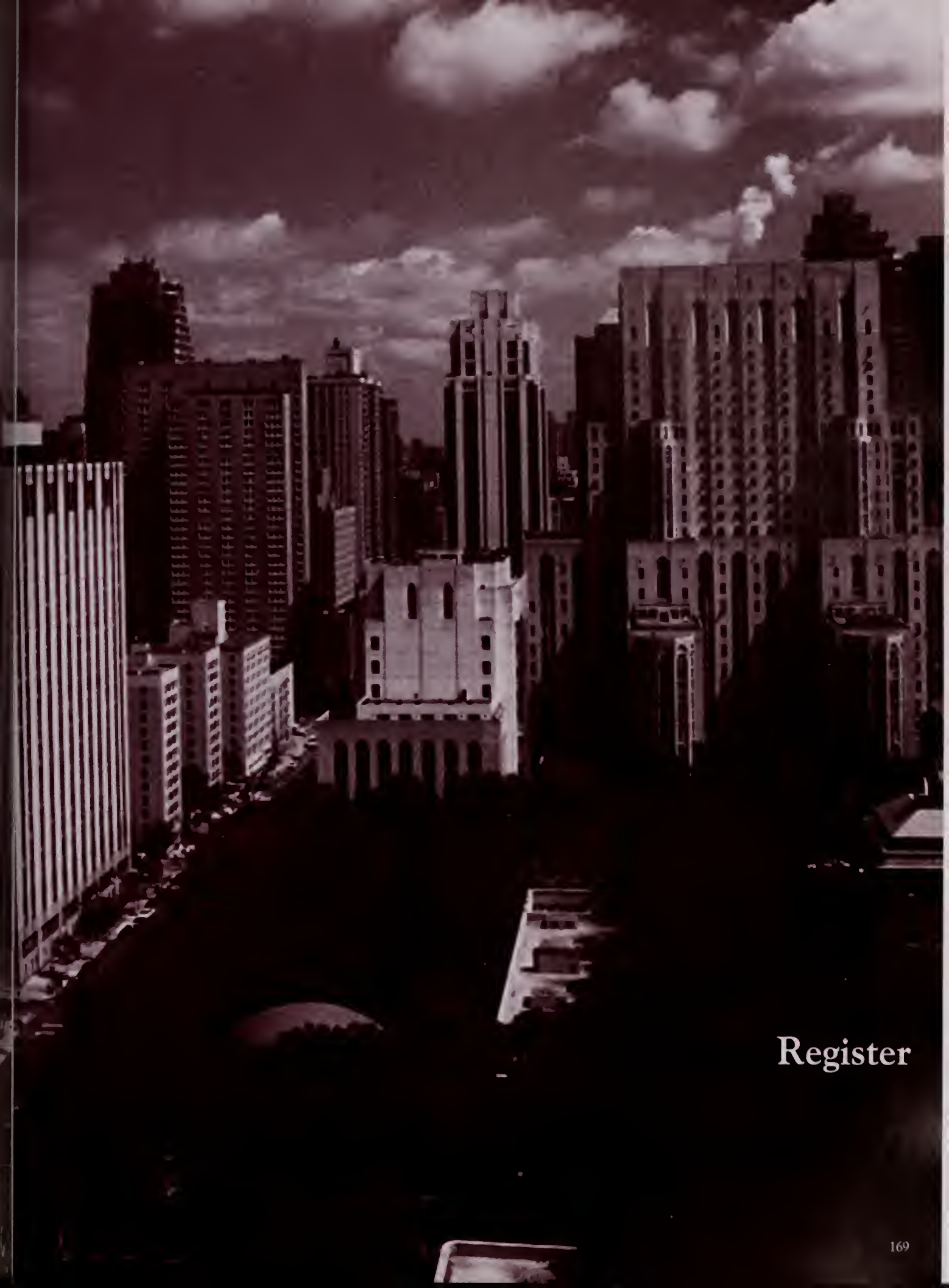
# Special Programs

## Ph.D.-M.D. Program

Ph.D. graduates of the Weill Graduate School of Medical Sciences of Cornell University may apply for admission to the Weill Medical College of Cornell University. A single admission per year from the Graduate School will be considered for highly qualified students. Graduate students in their third year of graduate training may apply for the Ph.D.-M.D. program through the Associate Dean of the Graduate School of Medical Sciences. A letter of request from the student and a letter of recommendation from the student's thesis advisor are required. If accepted into the program, students will complete four major courses of the first year medical school curriculum: Human Structure and Function; Genes and Development; Host Defenses; and Medicine, Physicians and Society, during years three, four, and five of graduate school. Pending successful completion, students may formally apply for admission to the Weill Medical College of Cornell University. Completion of coursework does not constitute a guarantee of acceptance to the medical college. If accepted, the Ph.D.-M.D. program student will enter the second year of medical school. Unlike the Ph.D. degree program, the M.D. degree program is not supported by scholarship, making it incumbent on the accepted student to assume financial responsibility for all tuition and living expenses.

## Cornell University Intercampus Student Exchange

Graduate students enrolled at the Weill Graduate School of Medical Sciences or at Cornell University in Ithaca may register for study with graduate faculty at either campus. Courses and research topics may be undertaken at either campus, depending on student need and resource availability.



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Pasternak, Gavril W. (Neuroscience, Pharmacology) Professor of Molecular Pharmacology and Therapeutics. Professor of Pharmacology. Professor of Neurology and Neuroscience. BA. 1969, M.D. 1973, Ph.D. 1974, Johns Hopkins University

Patel, Dinshaw J. (Biochemistry & Structural Biology) Professor of Biochemistry & Structural Biology. B.Sc. 1961, University of Bombay (India); M.S. 1963, California Institute of Technology; Ph.D. 1966, New York University

Pavletich, Nikola P. (Biochemistry & Structural Biology) Howard Hughes Medical Institute Associate Investigator. Professor of Biochemistry & Structural Biology. B.S. 1988, California Institute of Technology; Ph.D. 1991, Johns Hopkins University School of Medicine

Peterson, Margaret (Clinical Epidemiology) Associate Statistician in Medicine. B.Sc. 1960, Ph.D. 1967, Durham University (England)

Petrie, Howard T. (Immunology) Assistant Professor of Immunology. B.S. 1978, M.S. 1981, Pennsylvania State University; Ph.D. 1988, University of Nebraska Medical Center

Pickel, Virginia M. (Neuroscience) Professor of Neuroscience. B.S. 1965, M.S. 1967, University of Tennessee; Ph.D. 1970, Vanderbilt University

Pillemer, Karl (Clinical Epidemiology) Associate Professor of Human Development and Family Studies. B.A. 1977, Boston University; M.A. 1981, Ph.D. 1985, Brandeis University

Plum, Fred (Neuroscience) The Anne Parrish Titzell Professor of Neurology. B.A. 1944, Dartmouth College; M.D. 1947, Cornell University Medical College

Posner, Jerome B. (Neuroscience) Professor of Molecular Pharmacology and Therapeutics. Professor of Neurology and Neuroscience. B.S. 1951, University of Washington; M.D. 1955, University of Washington School of Medicine

Posnett, David Neil (Immunology) Associate Professor of Medicine. M.D. 1977, University of Geneva (Switzerland)

Ptashne, Mark (Molecular Biology) Professor of Molecular Biology. B.A. 1961, Reed College; Ph.D. 1968, Harvard University

Purpura, Keith (Neuroscience) Assistant Professor of Neuroscience. Ph.D. 1988, Rockefeller University

Reidenberg, Marcus M. (Pharmacology) Professor of Pharmacology. Professor of Medicine. M.D. 1958, Temple University School of Medicine

Reis, Donald J. (Neuroscience) The George C. Cotzias Distinguished Professor of Neurology. Professor of Neurology in Psychiatry. A.B. 1953, M.D. 1956, Cornell University Medical College

Resh, Marilyn D. (Cell Biology & Genetics, Biochemistry & Structural Biology) Professor of Cell Biology & Genetics, and of Biochemistry & Structural Biology. B.A. 1977, Princeton University; Ph.D. 1982, Harvard University

Rifkind, Arleen B. (Pharmacology) Professor of Pharmacology; Associate Professor of Medicine. B.A. 1960, Bryn Mawr College; M.D. 1964, New York University

Rifkind, Richard A. (Cell Biology & Genetics) Director, Sloan-Kettering Division, Professor of Cell Biology & Genetics. B.S. 1951, Yale University; M.D. 1955, Columbia University

Robbins, Laura (Clinical Epidemiology) Assistant Professor of Social Work in Medicine. B.S.W. 1979, City University of New York; M.S.W. 1984, Hunter College; D.S.W. 1994, Hunter College School of Social Work

Robertson, Hugh D. (Biochemistry & Structural Biology, Cell Biology & Genetics) Professor of Biochemistry. Professor of Cell Biology & Genetics. B.A. 1964, Harvard College; Ph.D. 1969, The Rockefeller University

Rodriguez, Eunice (Clinical Epidemiology) Assistant Professor, Field of Human Services Studies, and Field of Epidemiology. ATS 1978, University of Barcelona (Spain); MPH 1987, Dr.PH 1991 University of California, Berkeley, School of Public Health

Rodriguez-Boulan, Enrique (Cell Biology & Genetics, Neuroscience) Professor of Cell Biology and Anatomy. B.A. 1963, National College of Buenos Alres (Argentina); M.D. 1970, University of Buenos Aires (Argentina)

Rosen, Michael K. (Biochemistry & Structural Biology) Assistant Professor of Biochemistry & Structural Biology. B.S. 1987, University of Michigan; Ph.D. 1993, Harvard University

Rosen, Neal (Cell Biology & Genetics) Professor of Cell Biology & Genetics, Professor of Medicine. A.B. 1971, Columbia College; M.D., Ph.D. 1979, Albert Einstein College of Medicine

Rosenfeld, Myrna R. (Neuroscience) Assistant Professor of Neurology and Neuroscience. B.S. 1974, State University of New York at Stony Brook; M.S. 1978, Yeshiva University; Ph.D. 1981,Yeshiva University; M.D.1985, Northwestern University Medical School

Rothman, James E. (Cell Biology & Genetics, Biochemistry & Structural Biology) Professor of Cell Biology & Genetics and of Biochemistry & Structural Biology. B.A. 1971, Yale College; Ph.D. 1976, Harvard MedicalSchool

Ruchlin, Hirsch (Clinical Epidemiology) Professor of Economics in Public Health. B.A. 1963, Yeshiva College; M.A. 1965, Ph.D. 1968, Columbia University

Russo, Carlo (Immunology) Associate Research Professor of Immunology in Medicine. M.D. 1977, University of Genova Medical School (Italy)

Rutishauser, Urs (Cell Biology & Genetics). Professor of Cell Biology and Genetics. B.S. 1987, Brown University; Ph.D. 1973, The Rockefeller University

Ryan, Timothy A. (Biochemistry & Structural Biology, Neuroscience). Assistant Professor of Biochemistry. B.Sc. 1981, M.Sc. 1983 McGill University (Canada); M.S. 1986, Ph.D. 1989 Cornell University

Sadelain, Michel William Jeffrey (Immunology) Assistant Professor of Immunology. M.Sc., M.D. 1984, University of Paris (France); Ph.D. 1989, University of Alberta (Canada)

Salmon, Jane Eva (Immunology) Associate Professor of Medicine. A.B. 1972, New York University; M.D. 1978, College of Physicians and Surgeons, Columbia University

Sant'Angelo, Derek B. (Immunology) Assistant Professor of Immunology. B.S. 1986, University of Michigan at Ann Arbor; M.S. 1990, Rutgers University; Ph.D. 1993, Rutgers University and Robert Wood Johnson Medical School

Schattner, Elaine (Immunology) Assistant Professor of Immunology. B.A. 1982, Yale University; M.D. 1987, New York University School of Medicine

Scheinberg, David A. (Pharmacology) Associate Professor of Medicine and of Molecular Pharmacology and Therapeutics. A.B. 1977, Cornell University; M.D., Ph.D. 1983, Johns Hopkins University School of Medicine

Schwer, Beate (Molecular Biology) Assistant Professor of Microbiology. Dipl. 1984, Tubingen; Ph.D. 1989, EMBL Heidelberg

Scotto, Kathleen Weihs (Pharmacology) Associate Professor of Molecular Pharmacology and Therapeutics. B.S. 1977, St. John's University; Ph.D. 1983, Cornell University Graduate School of Medical Sciences

Shuman, Stewart (Molecular Biology, Biochemistry & Structural Biology) Professor of Molecular Biology and of Biochemistry & Structural Biology. B.A. 1976, Wesleyan University; M.D., Ph.D. 1983, Albert Einstein College of Medicine

Silver, Randi B. (Physiology, Biophysics & Molecular Medicine) Associate Professor of Physiology and Biophysics. B.A. 1979, Skidmore College; Ph.D. 1986, Brown University

Silverstein, Roy L. (Cell Biology & Genetics) Professor of Medicine. Professor of Medicine in Microbiology. Professor of Cell Biology & Genetics. B.S. 1975, Brown University; M.D. 1979, Emory University School of Medicine

Sirotnak, Francis M. (Pharmacology) Professor of Molecular Pharmacology and Therapeutics. B.S. 1950, University of Scranton; M.S. 1952, University of New Hampshire; Ph.D. 1954, University of Maryland

Smith, Gerard P. (Neuroscience) Professor of Psychiatry. B.S. 1956, St. Joseph's College; M.D. 1960, University of Pennsylvania

Smith, Kendall A. (Immunology) Professor of Medicine. B.S. 1964, Denison University; M.D. 1968, The Ohio State University College of Medicine

Söllner, Thomas H. (Cell Biology and Genetics) Assistant Professor of Cell Biology and Genetics. B.S., M.S. 1986, Ludwig-Maximilians-University, Munich (Germany); Ph.D. 1991, Ludwig-Maximilians-University, Munich (Germany)

Son, Jin H. (Neuroscience) Associate Research Professor of Neuroscience. B.S. 1978, Seoul National University (Korea); M.S. 1980, Korea Advanced Institute of Science and Technology; Ph.D. 1987, University of Iowa

Staiano-Coico, Lisa (Cell Biology & Genetics) Professor of Microbiology in Surgery. Professor of Cell Biology & Genetics. B.S. 1976, Brooklyn College of the City University of New York; Ph.D. 1981, Cornell University Graduate School of Medical Sciences

Stephenson, John L. (Physiology, Biophysics & Molecular Medicine) Professor of Biomathematics in Physiology and Biophysics. B.A. 1943, Harvard University; M.D. 1949, University of Illinois

Stokes, Peter E. (Neuroscience) Professor of Medicine, Professor of Psychiatry. B.S. 1948, Trinity College; M.D. 1952, Cornell University Medical College

Storey-Johnson, Carol (Clinical Epidemiology) Associate Professor of Clinical Medicine. B.S. 1973, Yale University; M.D. 1977, Cornell University Medical College

Sung, Ching-Hwa (Neuroscience, Cell Biology & Genetics) Assistant Professor of Ophthalmology in Cell Biology and Anatomy. Assistant Professor of Cell Biology & Genetics. B.S. 1984, National Taiwan University (Taiwan); Ph.D. 1989, National Yang-Ming Medical College (Taiwan)

Szatrowski, Ted (Clinical Epidemiology) Associate Professor of Medicine. B.A., B.S. 1977, M.D. 1983, University of Washington, Seattle

Szeto, Hazel H. (Pharmacology) Professor of Pharmacology. B.S. 1972, Indiana University; M.D. 1977, Cornell University Medical College; Ph.D. 1977, Cornell University Graduate School of Medical Sciences

Tate, Suresh S. (Biochemistry & Structural Biology) Professor of Biochemistry. B.Sc. 1958, M.Sc. 1960, University of Baroda (India); Ph.D. 1963, University of London (United Kingdom)

Tempst, Paul (Molecular Biology, Biochemistry & Structural Biology) Professor of Molecular Biology and of Biochemistry & Structural Biology. B.S. 1976, Ghent State University (Belgium); Ph.D. 1981, Ghent University (Belgium)

Thorson, Jon S. (Pharmacology, Biochemistry & Structural Biology) Assistant Professor of Biochemistry & Structural Biology. Assistant Professor of Molecular Pharmacology and Therapeutics. B.A. 1986, Augsburg College; Ph.D. 1993, University of Minnesota

Toth, Miklos (Pharmacology, Neuroscience) Assistant Professor of Pharmacology. M.D. 1977, Albert Szent-Gyorgyi Medical University (Hungary); Ph.D. 1985, Academy of Sciences (Hungary)

Trifletti, Rosario Richard (Neuroscience) Assistant Professor of Neurology and Neuroscience, Assistant Professor of Pediatrics. B.S. 1979, Seton Hall University; M.D. 1986, Johns Hopkins University School of Medicine; Ph.D. 1986, Johns Hopkins University School of Medicine

Trochim, Willliam M.K. (Clinical Epidemiology) Professor of Policy Analysis and Management. B.A. 1973, Mundelein College; M.A. 1975, Southern Connecticut University; Ph.D. 1980, Northwestern University

Victor, Jonathan D. (Neuroscience) Professor of Neurology and Neuroscience. B.A. 1973, Harvard University; Ph.D. 1979, The Rockefeller University; M.D. 1980, Cornell University Medical College

Volpe, Bruce T. (Neuroscience) Professor of Neurology and Neuroscience. B.S. 1969, Yale College; M.D. 1973, Yale University School of Medicine

Wagner, John Anthony (Neuroscience, Cell Biology & Genetics) Professor of Neurology and Neuroscience. Professor of Cell Biology and Anatomy. B.S. 1970, Loras College; Ph.D. 1975, Princeton University

Wang, Yi (Physiology, Biophysics and Molecular Medicine) Assistant Professor of Physics in Radiology. B.S. 1986, Fudan University (China); M.S. 1988, University of Wisconsin-Milwaukee; Ph.D. 1994, University of Wisconsin-Madison

Weinstein, Alan M. (Physiology, Biophysics & Molecular Medicine) Associate Professor of Physiology and Biophysics. Associate Professor of Medicine. A.B. 1971, Princeton University; M.D. 1975, Harvard University

Weksler, Marc E. (Immunology) The Irving Sherwood Wright Professor of Geriatrics in Medicine. B.A. 1958, Swarthmore College; M.D. 1962, Columbia University

Wiedmann, Martin (Cell Biology & Genetics) Associate Professor of Cell Biology & Genetics. Diploma and Staatsexamen 1975, University of Greifswald (Germany); Ph.D. 1979, University of Potsdam (Germany)

Williams-Russo, Pamela (Clinical Epidemiology) Associate Professor of Medicine. B.S. 1978, Harvard University; M.P.H. 1982, University of California, Berkeley; M.D. 1983, University of California, San Francisco

Wilson, Paul A. (Cell Biology and Genetics) Assistant Professor of Cell Biology and Genetics. B.A. 1980, Princeton University; M.Sc., 1982, London School of Economics (England); Ph.D., 1990, University of California Berkeley

Windhager, Erich E. (Physiology, Biophysics and Molecular Medicine) The Maxwell M. Upson Professor of Physiology and Biophysics. M.D. 1954, University of Vienna (Austria)

Wu, Hao (Biochemistry & Structural Biology) Assistant Professor of Biochemistry. B.Sc. 1985, Peking University (China); M.D. 1988, Peking University (China); Ph.D. 1992, Purdue University

Xu, Chanxing Wilson (Pharmacology) Assistant Professor of Pharmacology. B.Sc. 1984, Nanjing University (China); Ph.D. 1991, Massey University (New Zealand)

Zakim, David (Cell Biology & Genetics) The Vincent Astor Distinguished Professor of Medicine. Professor of Cell Biology & Genetics. B.A. 1956, Cornell University; M.D. 1961, State University of NewYork Downstate Medical Center

Zelenetz, Andrew (Molecular Biology) Assistant Professor of Medicine, Assistant Professor of Molecular Biology. A.B. 1977, Harvard University; M.D., Ph.D. 1984, Harvard Medical School

# Degree Recipients 1996-97

## DOCTORS OF PHILOSOPHY

Altun-Gultekin, Zeynep, M.D. 1985, University of Istanbul, Istanbul Facility of Medicine. Neuroscience, Professor John A. Wagner. Thesis: "Signal Transduction Mechanisms and the Role of Cytoskeleton in PC12 Migration: Regulation by SRC, RAS and RAS".

Bannish, Gregory, B.S., 1990, University of Massachusetts. Immunology, Professor Janet S. Lee. Thesis: "Transcriptional Regulation of MHC Class II Expression in Class II Negative B Cell Lines".

Brown, George Patrick, B.S. 1990, Fordham University. Neuroscience, Professor Gavril Pasternak. Thesis: "Identification of a Novel μ-Opioid Receptor Subtype for Morphine-6 -Glucuronide and Heroin".

Deng, Liang, B.S. 1991, University of Rochester. Molecular Biology, Professor Stewart Shuman. Thesis: "Mechanistic Studies of Vaccinia Virus Early Transcription".

Du, Shan, B.S. 1984, M.S., 1987, Peking University (People's Republic of China). Cell Biology and Genetics, Professor Paula Traktman. Thesis: "Studies on Vaccinia Virus DNA Replication Initiation: Identification of cis-Elements that are Required for Template Replication".

Ferguson, David Owen, B.S. 1988, University of Rochester. Molecular Biology, Professor William Holloman. Thesis: "DNA Repair by Homologous Recombination *Ustilago maydis*".

Ford, Renée D., B.S., 1989, Simmons College. Cell Biology & Genetics, Professor Joel D. Pardee. Thesis: "Identification and Isolation of an Autocrine Motility Factor from Lewis Lung Carcinoma Cells".

Giarre, Marianna, B.S. 1987, M.S. 1989, University of Geneva (Switzerland). Cell Biology & Genetics, Professor Anthony Brown. Thesis: "Studies of *Wnt*-1 Signal Transduction in Mammalian Cell".

Gibbs, Emma E., B.Sc., 1988, Auckland University. Molecular Biology, Professor Jerard Hurwitz. Thesis: "Studies of *In Vitro* DNA Replication and the Effects of Cell Cycle Regulators".

Gracy, Kimberly N., B.A. 1992, University of Texas. Neuroscience, Professor Virginia Pickel. Thesis: "The NMDA-type Glutamate Receptor in the Basal Forebrain: Ultrastructural Localization and Relationships with Neuromodulators".

Halaby, Issam Afif, B.S. 1987, American University of Beirut (Lebanon). Neuroscience, Professor William Pulsinelli. Thesis: "Induced Ischemic Tolerance and Changes in Gene Expression After Brief Ischemic Insults".

Heyrovska, Neela, B.Sc. 1990, M.Sc. 1992, Faculty of Natural Sciences, Charles University (Czechoslovakia). Molecular Biology, Professor Franz-Ulrich Hartl. Thesis: "Chaperone-Mediated Protein Folding in Mitochondria: Directionality of Hsp70 and Hsp60 Action".

Ho, Chong-Kiong, B.A., 1990, Rutgers University. Molecular Biology, Professor Stewart Shuman. Thesis: "Biochemical Characterization of Covalent Nucleotidyl-Transferases Encoded by *Chlorella* Virus PBCV-1 and a Double-stranded RNA Binding Protein Encoded by Vaccinia Virus".

Hoffman, Mary M., B.S., 1989, Ithaca College; M.S., 1992, Bucknell University. Pharmacology, Professor Paul D. Roepe. Thesis: "Mechanism of MDR Protein Mediated Multidrug Resistance".

Hom, Judith Seuk Han, B.S. 1990, Cornell University. Pharmacology, Professor David Scheinberg. Thesis: "The Characterization of OFQ/N Receptor on Human Lymphoma Cells".

Huh, Ho Young, A.B. 1992, Dartmouth College. Cell Biology & Genetics, Professor Roy Silverstein. Thesis: "Regulation of the Human Monocyte/Macrophage CD36 Expression".

Lemon, Bryan D., B.S., 1991, University of Delaware. Molecular Biology, Professor Leonard P. Freedman. Thesis: "Molecular Mechanisms of Gene Transcription by the Vitamin D3 Receptor".

Li, Bibo, B.S. 1990, Peking University (People's Republic of China). Molecular Biology, Professor Arthur Lustig. Thesis: "Regulation of Telomere Size in *Saccharomyces cerevisiae*".

Liang, Feng, B.S. 1988, Peking University (People's Republic of China). Cell Biology & Genetics, Professor Maria Jasin. Thesis: "Genetic Studies of Double-strand Break Repair in Mammalian Cells".

Liu, Qing, B.S. 1986, Nankai University (People's Republic of China). Biochemistry & Structural Biology, Professor Steven Gross. Thesis: "The Binding Sites of Nitric Oxide Synthases".

MacMicking, John D., M.S., 1991, The Australian National University. Immunology, Professor Carl Nathan. Thesis: "Targeted Mutagenesis of the Mouse Nitric Oxide Synthase 2 Locus and Characterization of Defects in Host Immunity".

Mao, BuQing, B.E. 1985, M.M. 1988, Shanghai Medical University (People's Republic of China). Neuroscience, Professor Jonathan Victor. Thesis: "The Intrinsic Dynamics of Retinal Bipolar Cells and Their Ion Channel Mechanisms".

Mao, Xiangdong, B.S. 1990, Fudan University (People's Republic of China). Molecular Biology, Professor Stewart Shuman. Thesis: "Biochemical and Genetic Characterization of RNA (Guanine-7-) Methyltransferase of Vaccinia Virus and Yeast".

Qiao, Jizeng, M.D. 1977, Beijing Second Medical College (People's Republic of China); M.A. 1991, Columbia University. Physiology & Biophysics, Professor Doris Herzlinger. Thesis: "Regulation of Renal Collecting System Morphogenesis".

Ryeom, Sandra Wonsuk, B.A. 1989, Wellesley College. Cell Biology & Genetics, Professor Roy Silverstein. Thesis: "Mechanisms of Phagocytosis by Retinal Pigment Epithelial Cells".

Sanchez, Juan P., Licenciado, 1989, Pontifica Universidad Catolica de Chile en Bioguimica. Molecular Biology, Professor Jerard Hurwitz. Thesis: "Isolation, Characterization and Molecular Cloning of a Protein (Abp2) that Binds to a *Schizosaccharomyces pombe* Origin of Replication (*ars*3002)".

Sankar, Usha, B.Sc. 1988, Kirori Mal College, Delhi University (India); M.Sc. 1990, Madurai Kamaraj University (India). Cell Biology & Genetics, Professor Paula Traktman. Thesis: "Protein Phosphorylation in Vaccinia Virus: Analysis of B1 Kinase and its Substrate, H5".

Steinberg, Douglas J., A.B. 1980, Princeton University. Neuroscience, Professor Ellen Townes-Anderson. Thesis: "The Processing of Abnormal APP and Tau: Implications for the Alzheimer's Disease Pathogenesis".

Tong, Youzhi, B.S. 1984, M.S. 1988, Peking University (People's Republic of China). Pharmacology, Professor Joseph Bertino. Thesis: "Isolation and Characterization of Mutants of Human Thymidylate Synthase Conferring Drug Resistance to Inhibitors of this Enzyme".

Wu, Xipu, B.M.Sc. 1988, Shanghai Medical University (People's Republic of China). Pharmacology, Professor John Mendelsohn. Thesis: "Cell Cycle and Cell Death Regulation by Epidermal Growth Factor Receptor Blockade".

Xuan, Shouhong, B.S. 1985, Sichuan University (People's Republic of China). Cell Biology & Genetics, Professor Eseng Lai. Thesis: "Winged-Helix Transcription Factor BF-1 Plays an Essential Role for the Development of the Cerebral Hemispheres by Regulating Cell Cycle Progression".

Zhong, Fengming, B.M. 1984, M.M. 1990, Zhejiang Medical University (People's Republic of China). Molecular Biology, Professor Michael Sheffery. Thesis: "Characterization of the Transcription Factor CP2".

Zhou, Wenjun, B.S. 1989, Fudan University (People's Republic of China). Cell Biology & Genetics, Professor Marilyn Resh. Thesis: "Membrane Targeting of HIV-1 Gag Proteins".

## MASTERS OF SCIENCE

Barden-Maja, Aba, B.A. 1988, Smith College; M.D., 1993, Yale University; Residency, 1995, Yale New Haven Hospital. Clinical Epidemiology, Professor Carol Mancuso. Master's Project Paper: "Psychosocial Factors and Outcomes of Hip Replacement Surgery".

Brown, Ellen, M.S. 1991, Columbia University; EDD, 1997, Columbia University Teachers' College. Clinical Epidemiology, Professor John Allegrante. Master's Project Paper: "A Study of a Side Rail Reduction Program in a Long-term Care Facility: Implications for a Professional Nursing Staff".

Li, Tao, B.S. 1988, Beijing Normal University (People's Republic of China). Immunology, Professor Janet S. Lee. Thesis: "Molecular Cloning of Transcription Factors Involved in MHC Class II Expression with Yeast Genetics".

Ling, Taotao, B.S. 1989, M.S. 1992, Peking University (People's Republic of China). Biochemistry and Structural Biology, Professor Paul Roepe. Thesis: "Acidosis During Apoptosis: Probing the Molecular Mechanism".

Keohane, Denis J., Internal Medicine Residency, 1992-1995, Brown University. Clinical Epidemiology, Professor Mary Charlson. Master's Project Paper: "Predictors of Progression of the Human Immunodeficiency Virus".

Quinn, Geoffrey, B.A., 1977, UCLA; MS.J., 1984, Columbia University; M.D., 1992, Cornell University Medical College. Clinical Epidemiology, Professor Pamela Williams-Russo. Master's Project Paper: "Intravenous Drug Users and Nitric Oxide Resistant Strains of TB: Could Overproduction of Macrophage-Derived iNOS Explain the Phenomenon?".

Westman, Sheila, B.A., 1994, Bard College. Pharmacology, Professor Lonny Levin. Thesis: "Functional Characterization of Rutabaga Adenylyl Cyclase Mutants".

Yu, Lei, B.A. 1994, Concordia College. Molecular Biology, Professor Stewart Shuman. Thesis: "Mutational Analysis of the Triphosphotase Component of Vaccinia Virus Capping Enzyme".

# Degree Recipients 1997-98

## DOCTORS OF PHILOSOPHY

Bose, Ron, B.A., B.S. 1991, University of Rhode Island. Pharmacology, Professor Richard Kolesnick. Thesis: "Utilization of the Second Messenger, Ceramide, by the Chemotherapeutic Agent Daunorubicin and the Reaper Protein during Induction of Apoptosis".

Cai, Jinsong, B.S. 1989, Sichuan University. Cell Biology & Genetics, Professor Jerard Hurwitz. Thesis: "Reconstitution and Characterization of Human Replication Factor C".

Chung, Sangmi, B.S. 1993, Seoul National University. Neuroscience, Professor Kathleen Scotto. Thesis: "Characterization of the Elav-like RNA binding proteins".

Crombie, Andrea Rene, B.A. 1981, Goucher College. Cell Biology & Genetics, Professor Roy Silverstein. Thesis: "Structural and Functional Characterization of Lysosomal Membrane Protein LIMP II: A CD36 Gene Family Member with Potential Roles in Cell Adhesion, Lipid Metabolism, and Metastasis".

Donovan, Gerald, B.S. 1993, University of California, Davis. Pharmacology, Professor Miklos Toth. Thesis: "Molecular Characterization of a Novel Epilepsy Gene".

Dyall, Rubendra, B.Sc. 1988, Bordeaux II University. Immunology, Professor Janko Nikolic-Zugic. Thesis: "The Use of Optimal MHC Class I-Binding Peptides to Study T Cell Selection, Recognition and Activation".

Egan, David A., B.Sc. 1991, University of Limerick. Neuroscience, Professor Kathleen Scotto. Thesis: "The Regulation of P-Glycoprotein Transcription by Steroid Hormone Receptors".

Fisher, Alfred Leo, B.S. 1991, Loyola Marymount University. Cell Biology & Genetics, Professor Michael Caudy. Thesis: "Hairy-Related bHLH Proteins and Runt Domain Proteins as Transcriptional Repressors that act through the Groucho Co-Repressor".

Gall, Jason G.D., B.S. 1990, University of California, Davis; M.S. 1992, University of California, Davis. Molecular Biology, Professor Erik Falck-Pedersen. Thesis: "The Role of Adenovirus Fiber and Hexon Proteins in Virus-Host Interactions".

Jin, Fenyu, B.M. 1990, Beijing Medical University. Immunology, Professor Carl F. Nathan. Thesis: "Differentially Expressed Genes between LPS Hyperresponsive and Hyporesponsive Macrophages: Secretory Leukocyte Protease Inhibitor as a LPS Response Inhibitor".

Li, Yong, M.B. 1991, Peking Union Medical College; Premed. 1988, Peking University. Molecular Biology, Professor Robert Benezra. Thesis: "Cloning and Characterization of hsMAD2, a Human Mitotic Checkpoint Gene".

Liu, Jiong, B.S. 1992, Rutgers University. Neuroscience, Professor Kenneth Marians. Thesis: "ØX-type Primosome Intersects Chromosome Replication and Recombination in *Escherichia Coli*".

Molano, Alberto, M.D. 1988, Colegio Mayor de Nuestra Senora del Rosario. Immunology, Professor Janko Nikolic-Zugic. Thesis: "Peptide Binding, TCR Recognition and Intrathymic Positive Selection by a MHC H-2K$^b$ Class I Molecule Devoid of the Central Anchor © Pocket".

Netzer, William J., B.S. 1971, Brooklyn College. Immunology, Professor Franz-Ulrich Hartl. Thesis: "Protein Folding during Translation: A Distinction between Eukaryotes and Prokaryotes Having Implications for the Evolution of Multidomain Proteins".

Newberger, Carol, B.A. 1979, Pomona College. Biochemistry & Structural Biology, Professor Elizabeth Lacy. Thesis: "The amn Gene Product is Required in Visceral Endoderm for the Generation of Middle Streak Derivatives".

Ng, Jenny Yik-Bing, B.Sc. 1987, The University of Calgary. Molecular Biology, Professor Kenneth J. Marians. Thesis: "The Stepwise Assembly of the ØX174-Type Primosome".

Niu, Hongwu, M.A. 1991, Peking University; B.S. 1988, Peking University. Molecular Biology, Professor Jerard Hurwitz. Thesis: "Characterization of Ku and the Effect of Ku on DNA".

Orlinick, Jason Richard, B.A. 1990, Washington University. Cell Biology & Genetics, Professor Moses V. Chao. Thesis: "Structure-Function Analysis of the Human FAS Receptor and Ligand".

Romanienko, Peter J., B.S. 1990, Fairleigh Dickinson University. Molecular Biology, Professor Maria Jasin. Thesis: "Expression of the Rare-Cutting Endonuclease, I-Sce I, in the Germline of the Mouse".

Ruan, Jia, B.S. 1992, Washington University. Immunology, Professor Carl F. Nathan. Thesis: "Macrophage-mediated Immunity and Microbial Resistance: $Ca^{2+}$/Calmodulin Regulation of Nitric Oxide (NO) Production and NO Resistance Genes from *Mycobacterium Tuberculosis*".

Stella, Gregory, B.S. 1987, Michigan State University. Immunology, Professor Peter Besmer. Thesis: "Cellular and Molecular Aspects of C-Kit Signaling in Mast Cells".

Towers, Terri Lynn, B.S. 1988, Lehigh University. Cell Biology & Genetics, Professor Leonard Freedman. Thesis: "Vitamin $D_3$-Mediated Repression of the Granulocyte-Macrophage Colony Stimulating Factor Locus".

Turner, Jennifer L., B.S. 1991, William Smith College. Molecular Biology, Professor Michael O'Donnell. Thesis: "The Use of the DNA Sliding Clamp in *E. coli* Replication: How the Clamp Loader Puts Rings onto DNA and How It Takes Them Off".

Vosseller, Keith Alan, B.A. 1987, Miami University. Molecular Biology, Professor Peter Besmer. Thesis: "Kit Signal Transduction in Bone Marrow Mast Cells".

Wan, Yong, M.S. 1990, Yunnan Normal University; B.S. 1983, Sichuan Agricultural University. Physiology & Biophysics, Professor Xin-Yun Huang. Thesis: "Role of Tyrosine Kinases in G-protein Signaling".

Weber, Lawrence W., B.S. 1991, Rensselaer Polytechnic Institute. Pharmacology, Professor Alan N. Houghton. Thesis: "Immunity to a Self Protein Expressed by Melanoma: Studies of DNA Immunization".

Weisburg, Jeffrey, B.A. 1991, Clarke University. Pharmacology, Professor David A. Scheinberg. Thesis: "Multidrug Resistance, Intracellular pH, and the Regulation of Immune Based Cytoxicity".

Wittschieben, John, B.A. 1990, Colgate University. Molecular Biology, Professor Stewart Shuman. Thesis: "DNA Transesterification by *Vaccinia* Topoisomerase I: Structure-Function Analysis through Targeted Mutagenesis".

Wolven, Amy K., B.A. 1992, Case Western University. Molecular Biology, Professor Marilyn D. Resh. Thesis: "The Role of the Acylated Amino-terminus of Fyn in Mediating Membrane Binding".

Yan, Wei, B.S. 1987, Peking University. Cell Biology & Genetics, Professor Robert Benezra. Thesis: "The Genetic Analysis of the 1d Genes in Mouse Development".

Zou, Hongyan, B.S. 1993, Brigham Young University. Cell Biology & Genetics, Professor Lee Ann Niswander. Thesis: "Distinct BMP Receptor Function in Limb Development".

## MASTERS OF SCIENCE

DeSilva, Heshani E., A.B. 1992, Mount Holyoke College. Cell Biology & Genetics, Professor Mary Ann Osley. Thesis: "Structure-Function Analysis of Hir 1, a Transcriptional Corepressor that Regulates Histone Gene Transcription in the *Saccharomyces Cerevisiae* Cell Cycle".

Hammel, Joyce R., B.A. 1995, Drew University. Neuroscience, Professor Teresa Milner. Thesis: "The Ultrastructural Changes in Hippocampal Neuropeptide Y Neurons Following Removal of Septal Cholinergic Inputs".

Harrison, Melanie, M.D. 1991, University of Connecticut School of Medicine; B.S. 1987, SUNY at Stony Brook. Clinical Epidemiology, Professor Pamela Williams-Russo. Master's Paper Project: "The Longitudinal Assessment of Cognitive Dysfuction in a Lupus Patient".

Loconti, Andrea, B.S. 1994, Syracuse University. Pharmacology, Professor Richard Kolesnick. Thesis: "Mechanism of Reaper Induced Apoptosis in the Absence of Sphingomyelin".

Safer, Michelle Laurie, B.A. 1994, Brandeis University. Pharmacology, Professor Ronald G. Blasberg. Thesis: "The Assessment of Ganciclovir Treatment in HSV1-tk Gene Transduced Tumors by Radiotracer Techniques".

White, Thomas, B.A. 1989, Oberlin College. Neuroscience, Professor Ronald Blasberg. Thesis: "Conjoint Attentional Switching Task: A Neuropsychological Probe for Assessing Set-shifting and Disinhibition in Autism".

Wu, Hong, B.S. 1991, William Smith College. Pharmacology, Professor Lorraine J. Gudas. Thesis: "Study of Homeobox Genes".

Yan, Jie-Shi, B.Sc. 1993, McMaster University. Cell Biology & Genetics, Professor Andrew Koff. Thesis: "P27 KIP1Accumulation during Terminal Differentiation in HL-60 Cells".

# Continuing Students 1998-99

## CANDIDATES FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

Adamo, Joan E. (Molecular Biology/Cell Biology & Genetics). B.S. 1996, Cornell University. Rochester, New York

Aghazadeh, Behzad (Physiology, Biophysics, & Molecular Medicine). Diplom 1995, Ludwig Maximillians University, (Germany). Tehran, Iran

Ahmed, Simi Tasnim (Immunology). B.A. 1995, Dartmouth College. Dhaka, Bangladesh

Amprey, Joseph Leonard (Molecular Biology/Cell Biology & Genetics). B.A. 1995, University of Pennsylvania. Baltimore, Maryland

Appleby, Susan Blixt (Molecular Biology/Cell Biology & Genetics). B.S. 1988, Rochester Institute of Technology. Albany, New York

Arndt, Michelle Lee (Pharmacology). B.S. 1995, University of Minnesota. Minneapolis, Minnesota

[3]Atherton, Ruth Elizabeth (Molecular Biology/Cell Biology & Genetics). B.A. 1993, University of California, Santa Barbara. Portland, Oregon

Bailey, Christopher (Neuroscience). B.A. 1997, Occidental College. Boulder, Colorado

Barton, William Alan (Molecular Biology/Cell Biology & Genetics). B.S. 1996, Virginia Commonwealth University. Fairfax, Virginia

Basu, Subham (Pharmacology). B.A. 1991, University of California, Berkeley. Noamundi, India

[1]Bence, Kendra Kathleen (Physiology, Biophysics, & Molecular Medicine). B.A. 1993, Colgate University. Ithaca, New York

Bennett, Richard Lynn (Molecular Biology/Cell Biology & Genetics). B.A. 1993, Kalamazoo College. Detroit, Michigan

Berman, Howard (Pharmacology). B.S. 1996, University of Michigan. Johannesburg, South Africa

Bernal, Alejandro (Physiology, Biophysics, & Molecular Medicine). B.S. 1995, University of Houston. Ottawa, Canada

Biggins, John (Pharmacology). B.S. 1989, Fordham University. North Tarrytown, New York

Birk, Alexander (Pharmacology). B.S. 1994, York College, St. Petersburg, Russia

Block, Ellen (Immunology). B.S. 1995, Massachusetts Institute of Technology. New York, New York

Bolan, Elizabeth (Neuroscience). B.S. 1991, University of Scranton. Haverhill, Massachusetts

[3]Bradsher, John Norman (Molecular Biology/Cell Biology & Genetics). B.S. 1989, Oklahoma Baptist University; M.S. 1990, University of Oklahoma. Broken Arrow, Oklahoma

Bromleigh, Virginia Carrington (Molecular Biology/Cell Biology & Genetics). B.A. 1987, M.S. 1990, New York University. Anaheim, California

Bullock, Stewart (Physiology, Biophysics, & Molecular Medicine). B.S. 1996, Indiana University. South Bend, Indiana

Burakov, Darya (Molecular Biology/Cell Biology & Genetics). B.A. 1994, Technion University (Israel); M.Sc. 1996, Weizman Institute (Israel). Moscow, Russia

Byrd, Cynthia Anne (Immunology). B.S. 1993, University of Maryland. Baltimore, Maryland

Cai, Hui (Molecular Biology/Cell Biology & Genetics). B.S. 1990, Sichuan University, (People's Republic of China). Fuzhou, People's Republic of China

Capiaux, Gina Marie (Pharmacology). B.A. 1991, California State University, Fresno. San Francisco, California

Carton, John Charles (Neuroscience). B.A. 1995, Johns Hopkins University. New York, New York

Castella, Paul Charles (Molecular Biology/Cell Biology & Genetics). B.S. 1987, University of London, (England). London, England

Chang, Pearl (Molecular Biology/Cell Biology & Genetics). B.A. 1993, University of California, Berkeley. Taipei, Taiwan

Chen, Lian (Pharmacology). B.S. 1994, Ohio State University. Suzhou, People's Republic of China

Chen, Xu (Biochemistry & Structural Biology). B.S. 1992, M.S. 1995, Tsinghua University (People's Republic of China). Yancheng, People's Republic of China

Chen, Yunbo (Neuroscience). B.S. 1995, Peking University (People's Republic of China). Yingkou, People's Republic of China

Cheng, Chonghui (Biochemistry & Structural Biology) B.M. 1990, Beijing Medical University (People's Republic of China); M.S. 1996, University of Notre Dam. People's Republic of China

Chesnutt, Catherine (Neuroscience). B.S. 1994, College of William and Mary. Columbia, South Carolina

[3]Chittka, Alexandra Nedlin (Neuroscience). B.A. 1985, Grinnell College. Leningrad, U.S.S.R.

Choe, Han Seok (Physiology, Biophysics, & Molecular Medicine) B.S. 1989, Seoul National University, (Korea). Seoul, Korea

Choe, Kwang-Min (Molecular Biology/Cell Biology and Genetics). B.S. 1992, Yonsei University (South Korea); M.S. 1996, New York University. Inchon, Korea

Cohen, Alona (Biochemistry and Structural Biology). B.A. 1997, University of California, Berkeley. Netanya, Israel

Courtney, Jody Catherine (Neuroscience). B.S. 1992, University of California, San Diego. Minneapolis, Minnesota

Crowe, Rebecca Lynn (Molecular Biology/Cell Biology and Genetics). B.S. 1994, Trenton State College. Hackensack, New Jersey

Das, Indranil (Neuroscience). B.A. 1993, Northwestern University. Calcutta India

Davis, Antonia (Neuroscience). B.A. 1994, University of Pennsylvania. Salem, Massachusetts

DeBellis, Robert (Neuroscience). B.A. 1997, Cornell University. New York, New York

[1]DeMasi, Joseph (Molecular Biology/Cell Biology and Genetics). B.S. 1995, Carnegie Mellon University. Port Chester, New York

Dimova, Dessislava Kostadinova (Molecular Biology/Cell Biology and Genetics). M.Sc. 1991, Sofia University, (Bulgaria). Sofia, Bulgaria

Domenech, Francesca (Pharmcology). B.A. 1995, Cornell University. New York, New York

[3]Dumitru, Calin Dan (Immunology). M.D. 1989, University of Medicine and Pharmacy (Romania). Iasi, Romania

Eubanks, Sharon Kay (Biochemistry and Structural Biology). B.S. 1980, University of Redlands. Fort Leavenwoth, Kansas

Fan, Wen (Immunology). B.S. 1990, Beijing Medical University (People's Republic of China). Xian, People's Republic of China

[1]Fang, Linhua (Molecular Biology/Cell Biology & Genetics). B.S. 1985, Zhejiang Medical University; M.S. 1989, Peking Union Medical College. Zhejiang, People's Republic of China

Gilbert, Mathew Timmerman (Physiology, Biophysics, & Molecular Medicine). B.A. 1990, Oberlin College. Ithaca, New York

Gillespie, Robert (Molecular Biology/Cell Biology & Genetics). B.S. 1994, University at Albany; M.S. 1997, University of Central Florida. Port Jefferson, New York.

Gitig, Diana Marcie (Molecular Biology/Cell Biology & Genetics). B.A. 1994, University of Pennsylvania. New York, New York

Glickstein, Sara Beth (Neuroscience). B.S. 1992, University of Pittsburgh. Sayre, Pennsylvania

Gorfajn, Barbara (Pharmacology). B.S. 1997, State University of New York, Binghamton. Brooklyn, New York

Greenfield, Jeffrey (Neuroscience). B.A. 1994, Amherst College. Brooklyn, New York

[1]Gu, Chengua (Molecular Biology/Cell Biology & Genetics). B.S. 1991, Beijing Agricultural University (People's Republic of China); M.S. 1993, Rutgers University. Beijing, People's Republic of China

Guger, Kathleen Ann (Molecular Biology/Cell Biology & Genetics). B.S. 1992, Carnegie Mellon University. Pittsburgh, Pennsylvania

Hamilton, Henry (Molecular Biology/Cell Biology & Genetics). B.S./B.A. 1995, Brigham Young University. St. George, Utah

Han, Hyunsil (Immunology). B.S. 1991, Yonsei University (Korea); M.S. 1997 San Diego Sate University. Seoul, Korea

Ho, Hao (Physiology, Biophysics, & Molecular Medicine). B.A. 1993, M.A. 1993, Washington University. Sabah, Malaysia.

Hohl, Tobias Martin (Molecular Biology/Cell Biology & Genetics). B.S. 1993, Duke University. Switzerland

Hsia, Constance (Molecular Biology/Cell Biology & Genetics). B.A. 1992, University of California, Berkeley. Lansing, Michigan

Huang, Wei (Physiology, Biophysics, & Molecular Medicine). B.S. 1993, M.S. 1995, University of Science and Technology (People's Republic of China). Chengdu, People's Republic of China.

Huard, Richard (Immunology). B.Sc. 1994, University of Guelph, (Canada). Ajax, Canada.

[3]Hyer, Jeanette D. (Molecular Biology/Cell Biology & Genetics). B.S. 1991, University of Connecticut. Massapequa, New York

Jacovina, Andrew (Biochemistry & Structural Biology). B.S. 1990, State University of New York at Stony Brook. Rockville Center, New York

Jiang, Licong (Biochemistry & Structural Biology). B.S. 1990, Tsinghua University, (People's Republic of China); M.S. 1994, University of Maryland, Fujian, People's Republic of China.

Jiang, Yun (Physiology, Biophyscis, & Molecular Medicine). B.S. 1993, Sichuan University (People's Republic of China). Wanxian, People's Republic of China

Jin, Shengkan (Pharmacology). B.S. 1992, Tsinghua University, (People's Republic of China). Hunan, People's Republic of China

Johnson, Robert Anthony (Neuroscience). B.A.1992, Johns Hopkins University; M.A. 1996, New York University. Brooklyn, New York.

Joo, Woo (Molecular Biology/Cell Biology & Genetics). B.A. 1993, Tufts University. Eoryung, South Korea

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Kalik, Steven (Neuroscience). B.S. 1994, Cornell University. New York, New York

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Kaufman, David (Immunology). B.A. 1994, Swarthmore University. Washington, District of Columbia

Kee, Kehkooi (Molecular Biology/Cell Biology & Genetics). B.S., M.S. 1997, Iowa State University. Sitiawan, Malaysia

Keller, Shannon Ann (Immunology). B.S. 1995, University of Maryland. Baltimore, Maryland.

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Kim, Edmund (Molecular Biology/Cell Biology & Genetics). B.A. 1994, Pomona College. Los Angeles, California

Kim, Karl H.S. (Neuroscience). B.S. 1989, Michigan State University. Seoul, Korea

[2]Kim, Seul-Ki (Molecular Biology/Cell Biology & Genetics). B.Sc. 1995, Seoul National University. Seoul, Korea

Kolinsky, Monica (Pharmacology). B.S. 1997, Moravian College. Easton, Pennsylvania

Krishna, Srikant (Biochemistry & Structural Biology). B.A. 1995, Johns Hopkins University. Nellore, India

Kuhlman, Julie Ann (Molecular Biology/Cell Biology & Genetics). B.Sc. 1989, University of Illinois at Urbana-Champaign. Ecket, Nigeria

Lampson, Michael (Physiology, Biophysics, & Molecular Medicine). A.B. 1994, Harvard University. Palo Alto, California

[3]Lee, Cynthia Ellen (Pharmacology). B.S. 1991, College of William and Mary. Washington, D.C.

Lee, Juliane (Physiology, Biophysics, & Molecular Medicine). B.A. 1989, Smith College; M.D. 1994, University of Wisconsin. Milwaukee, Wisconsin

Lee, Karen Myra (Physiology, Biophysics, & Molecular Medicine). B.A. 1993, Columbia University. Teaneck, New Jersey.

Lee, Ramee (Neuroscience). B.S. 1995, Duke University. Seoul Korea

Lehman, Kevin Scott (Neuroscience). B.S. 1991, Fordham University. Mt. Vernon, New York

Lennon, David (Physiology, Biophysics, & Molecular Medicine). B.A. 1993, Columbia University. Passaic, NJ.

[1]Leu, Frank Pou (Pharmacology). B.A. 1994, State University of New York, Binghamton. Kao-Shihn City, People's Republic of China

Levine, Cindy (Molecular Biology/Cell Biology & Genetics). B.S. 1990, Cornell University. Oceanside, NewYork

Li, Haiqing (Physiology, Biophysics, & Molecular Medicine). B.S. 1995, Beijing Medical University (People's Republic of China). Shanghai, People's Republic of China

Liao, Jack Chia-Fun (Pharmacology). B.A. 1994, University of California, Berkeley. Taipei, Taiwan.

Lin, Yixin (Biochemistry & Structural Biology). B.S. 1992, Peking University (People's Republic of China). Nanchong, People's Reupblic of China.

Liu-Chen, Xinyue (Neuroscience). B.A. 1992, Beijing Medical University (People's Republic of China). Beijing, People's Republic of China

Lowry, William (Molecular Biology/ Cell Biology & Genetics). B.S. 1996, University of Washington. Seattle, Washington

Lu, Yiran (Pharmacology). B.S. 1994, Tsinghua University (People's Republic of China). Jiangsu, People's Republic of China

Lum, Lawrence (Molecular Biology/Cell Biology & Genetics). B.A. 1993, University of California Berkeley. San Francisco, California

Lytle, Jennifer Robin (Biochemistry & Structural Biology). B.S. 1995, Clemson, University. Agana, Guam(U.S.A.)

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Magro, Pellegrino (Pharmacology). B.S. 1996, State University of New York, Stony Brook. New York, New York

Maksimova, Mayya (Pharmacology). B.S. 1995, St. Petersburg State University (Russia). St. Petersburg, Russia

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Markenson, Debbie Friedman (Pharmacology). B.A., A.A. 1995, Yeshiva University/Stern College. New York, New York

Markus, Maurice (Molecular Biology/Cell Biology & Genetics). B.S. 1993, Pennsylvania State University. Montgomery, Pennsylvania

May, Chad Michael (Immunology). B.S. 1993, University of Minnesota. Fridley, Minnesota

McAvoy, Thomas Andrew (Pharmacology). B.S. 1993, Virginia Polytechnic Institute and State University. Richmond, Virginia

McGrath, Melissa Suzanne (Immunology). B.S. 1996, Union College. Albany, New York.

Mei, Jianfeng (Neuroscience). B.Sc. 1985, M.Sc. 1988, Amoy University (People's Republic of China). Nanchang, People's Republic of China

Meneses, Patricio (Neuroscience). B.S. 1990, State University of New York at Stony Brook. Llay-Llay, Chile

Mennitt, Patricia Anne (Physiology, Biophysics, & Molecular Medicine). B.S. 1987, Alfred University; B.S.N. 1991, M.S.N. 1993, University ofVirginia. Brooklyn, New York

Messaoudi, Ilhem (Immunology). B.S. 1996, Lafayette College. Tunisia

Millard, Stanley Sean (Molecular Biology/Cell Biology & Genetics). B.A. 1993, Columbia University. Fort Eustis, Virginia

Mossessova, Elena (Molecular Biology/Cell Biology & Genetics). B.S. 1993, Moscow State Medical University (Russia); M.S. 1996, New York University. Russia.

[1]Nachman-Clewner, Michele (Neuroscience). B.Sc. 1989, The Hebrew University of Jerusalem (Israel). New York, New York

Neel, Olivia Davis (Biochemistry & Structural Biology). B.A. 1990, St. John College. New York, New York

Ngyuen, Hoang (Molecular Biology/Cell Biology & Genetics). B.A. 1991, Cornell University; M.S. 1995, Johns Hopkins University. Vietnam.

Nguyen, Kha Chi (Neuroscience). B.S., B.A. 1993, University of Rochester. Saigon, Vietnam

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[1]Noramly, Selina (Molecular Biology/Cell Biology & Genetics). B.A. 1992, St. Hilda's College, Oxford University (United Kingdom). Koala Lumput, Malaysia

[3]Ouyang, Honghai (Physiology, Biophysics, & Molecular Medicine). B.S. 1988, East China University of Chemical Technology. Changsha, People's Republic of China

Owyang, Alexander (Immunology). B.A. 1992, University of California, Berkeley. San Francisco, California

Park, Michele (Molecular Biology/Cell Biology & Genetics). A.B. 1994, Princeton University. Niagara Falls, New York

Pei, Yi (Molecular Biology/Cell Biology & Genetics). B.S. 1993, Nanjing University (People's Republic of China). Liu Zhi, People's Republic of China

Peng, Yufeng (Biochemistry & Structural Biology). B.S. 1993, University of Science and Technology of China (People's Republic of China). Chang Sha, People's Republic of China

[1]Pinto, Shirley (Neuroscience). B.A. 1988, M.S. 1992, New York University. Haifa, Israel

Poynor, Elizabeth (Molecular Biology/Cell Biology & Genetics). A.B. 1984, Princeton University; M.D. 1988, Columbia University. Nashville, TN.

Qin, Jie (Immunology). B.S. 1994, Peking University (People's Republic of China). Tianjin, People's Republic of China.

Quartarolo, Nicole Marie (Neuroscience). B.A. 1996, Rutgers University. Belleville, New Jersey.

1Rajasekaran, Sigrid Anne-Barbara (Physiology, Biophysics, & Molecular Medicine). Abitur 1986, Illertalgymnasium (Germany). Vohringen, Germany.

Ramirez-Montagut, Teresa (Immunology). M.D. 1997, University Nacional Autonoma de Mexico (Mexico). Mexico

Raspberry, Dara Folami (Molecular Biology/Cell Biology & Genetics). B.A. 1992, Harvard University. Bronx, New York

Recht, Judith (Molecular Biology/Cell Biology & Genetics). Lic. Biol. 1991, Universidad Simon Bolivar (Venezuela). Boston, Massachusetts

Roberts, Wendy Katherine (Physiology, Biophysics, & Molecular Medicine). B.A. 1996, Clark University. Waltham, Massachusetts.

Rodriguez-Moreno, Diana Virginia (Neuroscience). B. S. 1994, Universidade de Buenos Aires (Argentina). Buenos Aires, Argentina.

Rollins, Robert (Molecular Biology/Cell Biology & Genetics). B.A. 1992, Colgate University. Utica, NY

Rothschild, Gerson (Neuroscience). B.A. 1990, M.I.A. 1992, Columbia University. New York, New York

Rouzankina, Iaroslava (Molecular Biology/ Cell Biology & Genetics). M.Sc. 1995, Novosibirsk State University (Russia). Novosibirsk, Russia

Russo, Angelo (Pharmacology). B.S. 1997, State University of New York, Stony Brook. Queens, New York

Sanders, Quentin J. (Molecular Biology/Cell Biology & Genetics). B.S. 1996, Lander University. Athens, Georgia.

Schaffer, Andras (Immunology). M.D. 1993, University Medical School of Pecs (Hungary). Celldomolk, Hungary.

Schlondorff, Johannes (Molecular Biology/Cell Biology & Genetics). B.S. 1994, Harvard University. Bronx, New York

Shen, Jian (Physiology, Biophysics & Molecular Medicine). B.A. 1992, Tsinghua University. Poyang, Henan Province, People's Republic of China

Shiloh, Michael Uri (Immunology) B.S. 1993, Pennsylvania State University. Montgomery, Pennsylvania

Sibille, Etienne (Pharmacology). B.S. 1994, Ramapo College. Mulhouse, France.

Sinclair, Meeghan (Neuroscience). B.A. 1992, Hunter College. Jersey City, New Jersey

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Soos, Timothy Jon (Molecular Biology/Cell Biology & Genetics). B.A. 1990, Middlebury College. Long Beach, New Jersey

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Staeva, Teodora Petrova (Immunology). B.A. 1995, Macalester College. Sofia, Bulgaria.

Stebbins, Charles Erec (Biochemistry & Structural Biology). B.S. 1992, Oberlin College. Lincoln, Nebraska

Su, Wendy (Pharmacology). B.A. 1994, Colgate University. Kanshiung, Taiwan.

Suh, Eun-Kyung (Neuroscience). B.A. 1994, Wellesley College. Seoul, Korea

Suldan, Zalman L. (Molecular Biology/Cell Biology & Genetics). B.A. 1989, University of Pennsylvania. Pittsburgh, Pennsylvania

Tai, Andrew Wen-Yuan (Molecular Biology/Cell Biology & Genetics). A.B. 1994, Harvard University. Manitoba, Canada

Talati, Ardesheer (Pharmacology). B.A. 1995, Grinnell College. Karachi, Pakistan.

[3]Thayer, Sarah Perry (Neuroscience). B.A. 1985, Earlham College; M.S. 1987, Georgetown University; M.D. 1991, University of Virginia School Medicine, Tokyo, Japan

Thompson, Chad (Molecular Biology/Cell Biology & Genetics). B.S. 1995, Towson State University. Wilmington, Delaware

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Torigoi, Emi (Molecular Biology/Cell Biology & Genetics). B.S. 1992, Universidade Estaduale de Campinas (Brazil); M.S. 1996, University of Sao Paulo (Brazil). Sao Paulo, Brazil.

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Tourigny, Michelle Renee (Immunology). B.A. 1992, College of the Holy Cross. Gardner, Massachusetts

Trevejo, Jose Miguel (Molecular Biology/Cell Biology & Genetics). B.S. 1994, University of California. San Bernardino, California

Tritel, Marc (Molecular Biology/Cell Biology & Genetics). A.B. 1991, Harvard University. Philadelphia, Pennsylvania

Tsai, Jeffrey Jen-Chieh (Neuroscience). B.S.E. 1993, Duke University. Kaohsiung, Taiwan

Tumang, Joseph (Immunology). B.S. 1994, Regents College. Quezon City, Philippines

Turner, Brian (Neuroscience). B.S. 1990, Curtin University. Perth, Australia.

Vakiani, Efsevia (Pharmacology). A.B. 1993, Harvard University. Thessaloniki, Greece

Varma, Anjali (Molecular Biology/Cell Biology & Genetics). B.S. 1994, Pennsylvania State University. Bloomington, Indiana

Vijayvergiya, Chetan (Molecular Biology/Cell Biology & Genetics). B.S. 1994, University of Texas. Houston, Texas

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Ward, Jeremy Ogden (Molecular Biology/Cell Biology & Genetics). B.A. 1994, Cornell University. New Haven, Connecticut

Wright, Anne Mythue (Neuroscience). B.S. 1993, Georgetown University. Aarthus, Denmark

Wu, George (Molecular Biology/Cell Biology & Genetics). B.A. 1992, University of California, Berkeley; M.A. 1994, Stanford University. Taipei, Taiwan

Wysocki, Carrie (Physiology, Biophysics, & Molecular Medicine). B.A. 1997, New York University. Syracuse, New York

Xu, Juliana (Pharmacology). B.S. 1997, Grove City College. Tianjin, China

Xu, Lei-Wei (Biochemistry & Structural Biology). B.S. 1984, Nanjing Normal University (People's Republic of China). Changzhou, People's Republic of China

Yang, Haijuan (Pharmacology). B.S. 1993, Beijing Medical University (People's Republic of China); M.S. 1996, University of Arkansas. Tianjin, People's Republic of China

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Young, Zuyung Alison (Immunology). B.A. 1992, Rutgers University. Taiwan

Yousef, Diana (Biochemistry & Structural Biology). A.B. 1994, Harvard University. Boston, Massachusetts

Zhang, Congxiao (Neuroscience). B.S. 1987, M.S. 1990, Peking University. Beijing, People's Republic of China

Zhang, Xiaowei (Molecular Biology/Cell Biology & Genetics). M.D. 1988. Shanghai Medical University (People's Republic of China). Shanghai, People's Republic of China

Zhu, Jing (Pharmacology). B.S. 1993, Beijing Medical University (People's Republic of China); M.S. 1995, University of Connecticut Health Center. Beijing, People's Republic of China.

Zirvi, Monib A. (Molecular Biology/Cell Biology & Genetics) B.S.E. 1993, Princeton University. Bergen, New Jersey

## CANDIDATES FOR THE DEGREE OF MASTER OF SCIENCE

Boockvar, Kenneth (Clinical Epidemiology). B.A. 1989, Harvard University; M.D. 1993, Duke University. Queens, New York

Boutin, Carla (Clinical Epidemiology). B.A. 1990, New York University; M.D. 1994, Brooklyn College. Haiti

Fukuda, Seiya (Neuroscience). B.S. 1994, California Institute of Technology. East Patchogue, New York

Liu, Franklin (Molecular Biology). B.A. 1993, Colgate University. New Brunswick, New Jersey

Pacheco, Paul (Clinical Epidemiology). B.S. 1989, Boston College; M.D. 1993, Brown University School of Medicine. Azores, Portugal

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[1] in absentia
[2] leave of absence
[3] candidate for degree only

# Entering Students 1998-1999

Alcid, Alston Dean (Molecular Biology/Cell Biology & Genetics). B.S. 1998, The College of New Jersey. Paramus, New Jersey

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Bogulavsky, Johanna Julie (Neuroscience). B.M. 1993, Northwestern University. New York, New York

Chen, Jian (Pharmacology). B.S. 1997, Tsinghua University (People's Republic of China). Zhejiang, China

Chmielnicki, Eva Janet (Neuroscience). B.A. 1998, University of Pennsylvania. Bronx, New York

Cox, Virginia Taylor (Molecular Biology/Cell Biology & Genetics). B.S. 1998, Wake Forest University. Raleigh, North Carolina

Dahlen, Karl Anna (Neuroscience). B.S. 1996, Brown University. Moraga, California

Do, Gian (Immunology). B.S. 1990, Cornell University. Vietnam

Du, Zhemei (Immunology). M.D. 1993, Beijing Medical University (People's Republic of China). Beijing, China

Gamble, Matthew Jon (Molecular Biology/Cell Biology & Genetics). B.A. 1998, Rutgers University. Milford, New Jersey

Gonzalez, Katie Nicole (Molecular Biology/Cell Biology & Genetics). B.A. 1995, Ginnell College. San Diego, California

Hao, Gang (Pharmacology). B.S. 1997, Nankai University (People's Republic of China). Tianjin, China

Hseih, Anita Yuan-Fan (Molecular Biology/Cell Biology & Genetics). B.A. 1998, Columbia University. Parsippany, New Jersey

Hu, Xiaoyu (Immunology). B.M. 1997, Beijing Medical University (People's Republic of China). Beijing, China

Huang, Yihua (Physiology, Biophysics, & Molecular Medicine). B.S. 1995, Peking University (people's Republic of China). Shaoyang, China

Kelly, Kristine Ann (Molecular Biology/Cell Biology & Genetics). B.A. 1998, Tufts University. Rumson, New Jersey

Kim, Sunjung (Immunology). B.S. 1995, Seoul Women's University (Korea). Seoul, Korea

Kreishman, Mara (Biochemistry & Structural Biology). B.S. 1998, University of Cincinnati. Cincinnati, Ohio

Lee, Mona Duh-Wei (Pharmacology). B.A. 1992, University of California, Berkeley. Brea, California

Lindwasser, Onn Wolf (Molecular Biology/Cell Biology & Genetics). B.S. 1998, Hunter College. New York, New York

Link, Lilli Beth (Clinical Epidemiology). M.D. 1994, University of Chicago. New York, New York

Litvin, Tatiana (Pharmacology). B.A. 1998, Clark University. St. Petersburg, Russia

Lo, Roger (Molecular Biology/Cell Biology and Genetics). B.S. 1994, Stanford University. Republic of China

Lou, Olivia (Immunology). B.Sc. 1997, University of Alberta (Canada). Edmonton, Canada

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Meehl, Michael Alan (Pharmacology). B.S. 1998, Cornell University. Johnson City, New York

Mody, Roshni (Pharmacology). B.S. 1996, Carnegie Mellon University. New York, New York

Moench, Paul Andrew (Pharmacology). B.S. 1998, SUNY Stony Brook. Selden, New York

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Sawaya, Rana (Molecular Biology/Cell Biology & Genetics). B.Sc. 1998, McGill University (Canada). Montreal, Canada

Seto, Jeremy (Neuroscience). B.A. 1998, Rutgers College. Queens, New York

Shen, Lijian (Physiology, Biophysics, & Molecular Medicine). B.S. 1997, Peking University (People's Republic of China). Beijing, China

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